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ENDOGENOUS NITRIC OXIDE AND DOPAMINE REGULATE FEEDING BEHAVIOR IN NEONATAL LAYER-TYPE CHICKENS

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Abstract

Evidence from animal studies suggests that endogenous nitric oxide and dopamine (DA) have a regulatory role in the rewarding system, but their interaction(s) have not been studied in avian species. In this study, 4 experiments were performed to determine the effects of central administration of L-arginine (nitric oxide precursor; 200 nmol), N^G-nitro-L-arginine methyl ester (L-NAME, a nitric oxide synthase inhibitor; 100 nmol), amphetamine (an indirect DA agonist; 125 pmol) and DA (40 pmol) on feeding behavior in neonatal layer-type chickens (each experiment included 4 groups, n=12 birds in each group). Prior to the initiation of the treatments, birds were fasted for 3 hours (FD3). In experiment 1, chickens received intracerebroventricular (ICV) injection of saline, L-NAME (100 nmol), amphetamine (125 pmol), and combination of L-NAME + amphetamine. In experiment 2, chickens received the ICV injection of saline, L-arginine (200 nmol), amphetamine (125 pmol) and their combination. In experiment 3, chickens received ICV injection of saline, L-arginine (200 nmol), DA (40 pmol) and L-arginine + DA. In experiment 4, chickens received ICV injection of saline, L-NAME (100 nmol), DA (40 pmol) and L-NAME + DA. Thereafter, the cumulative food intake (on the basis of metabolic body weight) was recorded until 2-h post injection. The results showed that ICV injection of amphetamine or DA significantly decreased food intake ($P<0.05$). Also, co-administration of L-NAME + amphetamine attenuated the hypophagic effect of amphetamine ($P<0.05$), while combined administration of L-NAME and DA had no effect on DA-induced hypophagia. Additionally, the hypophagic effect of amphetamine was significantly amplified by L-arginine ($P<0.05$), but the combination of L-arginine and DA did not alter feeding behavior which was induced by DA. These results suggest an interaction between DAergic and nitrergic systems via a presynaptic mechanism on food intake regulation in layer-type chicken.

Key words: endogenous nitric oxide, dopamine, food intake, layer-type chicken

Complex neurochemical pathways are involved in many parts of the brain to modulate appetite such as the striatum, hypothalamus and amygdala. To date, numerous neuropeptides and neurotransmitters have been discovered in the brain, where food intake is regulated (Boswell, 2005). Many features of central food intake regulation in birds are similar to mammals but there are some variations in the neurochemical processes between them (Zendehdel and Hassanpour, 2014 a). L-arginine is a metabolically versatile amino acid in many animal cells, giving rise to nitric oxide (NO) (Morris, 2004). NO, a free radical gas, is a highly reactive signaling molecule which could be synthesized by nitric oxide synthases (NOS) from L-arginine and works as a neurotransmitter. Three major subtypes of NOS are classified: neuronal NOS (nNOS), endothelial NOS (eNOS) and the inducible NOS (iNOS) (Guix et al., 2005). The NO has a regulatory role in food intake in the central nervous system (CNS). The ICV injection of NOS inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), decreased food intake in rats (De Luca et al., 1995). Central injection of L-arginine increased food intake in mice (Morley and Flood, 1991) while acting as a feeding-inhibitory agent in layers (Khan et al., 2007). ICV administration of L-NAME amplified food intake in layer-type chickens (Hassanpour et al., 2015) while it had no effect in meat-type chicks (Khan et al., 2007).

Dopamine is the main catecholamine neurotransmitter in the CNS, which plays a critical role in locomotor activity, cognition, emotion, positive reinforcement and food intake (Zendehdel and Hassanpour, 2014 b). The role of the DAergic system in mammals and avian neural processes has been documented extensively for many years. Previously, Volkow et al. (2011) reported that central injection of D_1 and D_2 agonist diminishes food intake in rat. In contrast, DA-induced hypophagia is mediated by D_1 receptors in chicken while other receptors (D_2, D_3 and D_4) may have no role in appetite regulation (Zendehdel et al., 2014 a).

Several experiments have shown that relationships exist between the nitrergic and DAergic systems. Dopamine signaling in the hypothalamus appears to be mediated via neurons in the dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), lateral hypothalamus (LH), nucleus accumbens (NAcc) and arcuate nuclei (ARC) (Guy et al., 2011). In the brain, NO has been linked to release and uptake of the DA as well as several behavioral pathologies involved with DAergic imbalance, like Parkinson's disease, schizophrenia and drug addiction (Salum et al., 2008). An interaction was reported between NO, DA, amphetamine and cocaine (Salum et al., 2006; 2008). The ICV injection of L-NAME reduced the release of the DA (Liu, 1996). For instance, L-arginine regulates post synaptic DA release by NO (Volz et al., 2004). On the other hand, amphetamine-induced behaviors are modulated by NO inhibitor in rats (Salum et al., 2008). In a similar study it was shown that NO synthase inhibitor, N G-nitro-L-arginine (L-NOARG) interacts with amphetamine (indirect DA agonists) but not with the direct DA agonists on prepulse inhibition in rat. Perhaps there is a presynaptic pathway between nitrergic and DAergic neurons (Salum et al., 2006).

Arcuate nucleus (ARC) is a target site for signals regulating energy homeostasis (Shiraishi et al., 2008). Electrophysiological and immunohistological studies demonstrated that the NO signaling pathways within the ARC contribute to appetite

regulation, possibly interacting with other pathways where neuropeptide Y (NPY)/ agouti related protein (AgRP) and pro-opiomelanocortin (POMC) and cocaine/amphetamine regulated transcript (CART) expressing neurons are regionally clustered (Riediger et al., 2006). In contrast, the DA interacts with DMH and ARC neurons (Zendehdel et al., 2014). Hence, NO interacts with many neuropeptides like the NPY (Morley et al., 2011). The neuroendocrine control of food intake and energy balance is a complex process controlled by many overlapping integrated pathways (McCormack and Denbow, 1989).

So far, numerous studies have been done to determine the effects of neurotransmitters on feeding behavior in mammals, but aspects of food intake regulation in avian species still remain unclear (Alizadeh et al., 2015). Given the estimated 300 million years of evolutionary distance between mammals and avian, it is not surprising that significant differences have been found in the activities of a number of components involved in energy homeostasis (Novoseletsky et al., 2011). To our best knowledge, there are no data about the influence of the NO on DA-induced hypophagia in layer-type chicken. Based on findings in the earlier literature and considering that NO and DA have the same effects on some physiological processes, the goal of the current study was to investigate the possible interaction of nitrergic and DAergic systems on feeding behavior in food deprived (FD_3) neonatal layer-type chickens.

Material and methods

Animals

A total of 176 one-day-old female layer-type chickens were purchased from a local hatchery (Seamorgh Co., Iran). Birds were maintained in stabilized electrically heated batteries at a temperature of 32ºC±1, kept at 40–50% relative humidity and 23:1 lighting/dark period (Olanrewaju et al., 2006). Birds were kept for 2 days as flock and then randomly allocated into their individual cages. A commercial starter diet containing 21% crude protein and 2850 kcal/kg metabolizable energy (Animal Science Research Institute of Iran) was provided to animals. During the course of study all birds had *ad libitum* access to diet and fresh water. Three hours 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) and the current laws of the Iranian government for animal care.

Experimental drugs

Drugs used in this study including L-arginine hydrochloride (L-Arg) (nitric oxide precursor), N^G-nitro-L-arginine methyl ester (L-NAME, nitric oxide synthase inhibitor), amphetamine (an indirect DA agonist), DA and Evans blue were purchased from Sigma Co. (Sigma, USA). Drugs were dissolved in absolute dimethyl sulfoxide (DMSO) and then diluted with 0.85% saline containing Evans blue at a ratio of 1/250

(0.4% DMSO). DMSO with this ratio does not have a cytotoxic effect (Blevins et al., 2002; Qi et al., 2008).

ICV injection procedures

Birds were allocated into experimental groups based on their body weight. Thus, the mean body weight between treatment groups was as uniform as possible. To determine the possible interaction between endogenous nitric oxide and DAergic systems on food intake, 4 experiments were designed, each including 4 treatment groups within 11 replicates in each group (n=44 birds per experiment). The birds were injected intracerebroventricularly once in each experiment using a microsyringe (Hamilton, Switzerland) without anesthesia in accordance with Davis et al. (1979) and Furuse et al. (1997). In this technique, head of the birds 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 that was located over the skull immediately over the 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). Each chicken was injected with control or drug solution in a volume of 10 µL. 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 chickens 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. Twelve birds in each group received injections, but the analysis only used data from individuals in which the dye was present in the lateral ventricle (9 to 12 chickens per group). All experimental procedures were done from 8:00 A.M. until 15:30 P.M.

Feeding experiments

In this study, 4 experiments were designed, each with 4 treatment groups (n=48 in each experiment). In experiment 1, four groups of the FD_3 chicks received a dose of either the ICV injection of A: control solution, B: L-NAME (100 nmol), C: amphetamine (125 pmol), D: combination of L-NAME + amphetamine. In experiment 2, group A: ICV injected with saline, B: L-arginine (200 nmol), C: amphetamine (125 pmol), D: combination of L-arginine + amphetamine. In experiment 3, FD_3 chicks received an ICV injection of control solution (A), L-B: NAME (100 nmol), C: DA (40 pmol), D: L-NAME + DA. In experiment 4, group A: ICV injected with saline, B: L-arginine (200 nmol), C: DA (40 pmol), D: L-arginine + DA. Details of the injection procedures are given in Table 1. Control groups were ICV injected with 10 µL saline containing Evans blue. Each bird was injected once only. These doses of drugs were determined according to the previous (Khan et al., 2007, 2008; Zendehdel et al., 2014 b; Alimohammadi et al., 2015) and pilot studies (unpublished). Right after injection, chickens were returned to their individual cages and provided *ad libitum* food (pre-weighed) and water, then cumulative food intake was recorded at 30, 60 and 120 minutes post injection. Food consumption was calculated on the basis of the percentage of body weight to adjust the differences between individuals.

Table 1. Experimental design 1–4

Exp. 1	
Treatment groups	ICV Injection
A	Saline
B	L-NAME (100 nmol)
C	Amphetamine (125 pmol)
D	L-NAME (100 nmol) + amphetamine (125 pmol)
Exp. 2	
Treatment groups	ICV Injection
A	saline
B	L-arginine (200 nmol)
C	Amphetamine (125 pmol)
D	L-arginine (200 nmol) + amphetamine (125 pmol)
Exp. 3	
Treatment groups	ICV Injection
A	Saline
B	L-NAME (100 nmol)
C	Dopamine (40 pmol)
D	L-NAME (100 nmol) + dopamine (40 pmol)
Exp. 4	
Treatment groups	ICV Injection
A	Saline
B	L-arginine (200 nmol)
C	Dopamine (40 pmol)
D	L-arginine (200 nmol), dopamine (40 pmol)

L-arginine: nitric oxide precursor, L-NAME: N^G-nitro-L-arginine methyl ester, a nitric oxide synthase inhibitor, amphetamine: indirect dopamine agonist.

Statistical analysis

Cumulative food intake was analyzed by a two-way analysis of variance (ANOVA) for repeated measurement. Data were presented as the mean ± SEM. For treatments found to have an effect, according to the ANOVA, mean values were compared with *post hoc* Tukey-Kramer tests. P-values <0.05 were considered to indicate significant differences between the treatments.

Results

The food intake response to role of L-arginine/NO pathway and DA interaction on feeding behavior in neonatal layer-type chicks are shown in Figures 1, 2, 3, and 4. In Experiment 1, ICV injection of L-NAME (100 nmol) had no significant effect on food intake in comparison with control group ($P>0.05$). ICV injection of amphetamine (DA agonist, 125 pmol) significantly decreased food intake compared

to control group in chickens (P<0.001). Also, co-administration of L-NAME plus amphetamine significantly decreased hypophagic effect of amphetamine in chickens [treatment effect: F (3, 80) = 49.71, P< 0.001; time effect: F (2, 80) = 142.8, P<0.001; treatment and time interaction: F (6, 80) = 5.48; P<0.001; Figure 1].

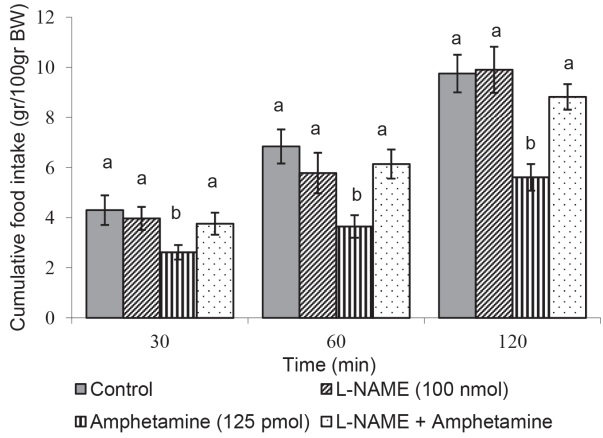

Figure 1. Effect of ICV injection of L-NAME (100 nmol), amphetamine (125 pmol) and their combination on percent of metabolic cumulative food intake in neonatal layer type chickens. L-NAME: nitric oxide antagonist, amphetamine: indirect dopamine agonist. There are significant differences between groups with different superscripts in a column (a and b; P<0.05) (treatment effect: F (3, 80) = 49.71, P<0.001; time effect: F (2, 80) = 142.8, P<0.001; treatment and time interaction: F (6, 80) = 5.48; P<0.001)

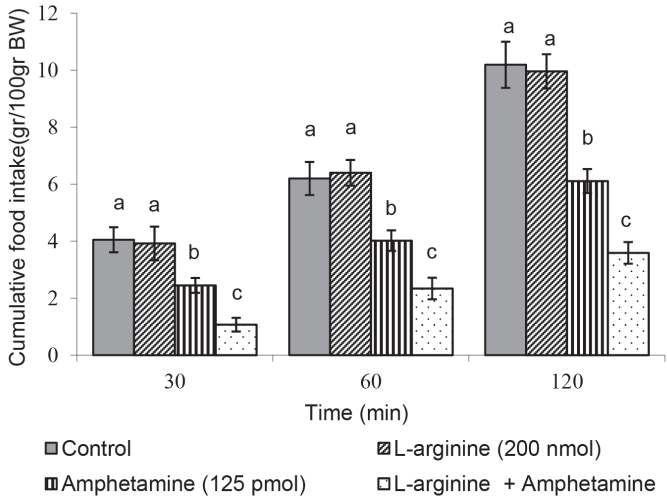

Figure 2. Effect of ICV injection of L-arginine (200 nmol), amphetamine (125 pmol) and their combination on percent of metabolic cumulative food intake in neonatal layer type chickens. L-arginine: nitric oxide precursor, amphetamine: indirect dopamine agonist. There are significant differences between groups with different superscripts in a column (a, b and c; P<0.05) (treatment effect: F (3, 80) = 57.13, P<0.001; time effect: F (2, 80) = 137.4, P<0.001; treatment and time interaction: F (6, 80) = 4.27; P<0.001)

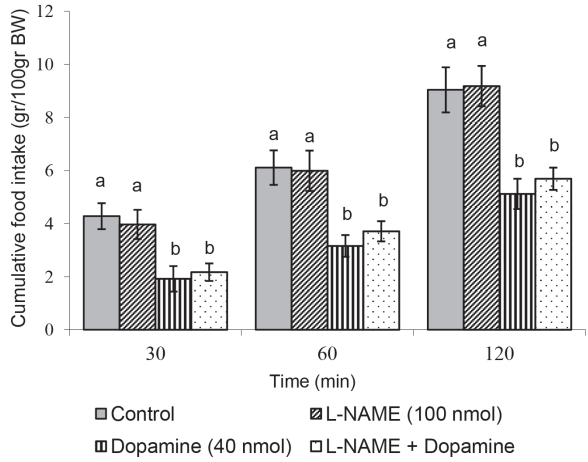

Figure 3. Effect of ICV injection of L-NAME (100 nmol), dopamine (40 pmol) and their combination on percent of metabolic cumulative food intake in neonatal layer type chickens. L-NAME: nitric oxide antagonist. There are significant differences between groups with different superscripts in a column (a and b; P<0.05) (treatment effect: F (3, 80) = 96.24, P<0.001; time effect: F (2, 80) = 173.8, P<0.001; treatment and time interaction: F (6, 80) = 6.31; P<0.001)

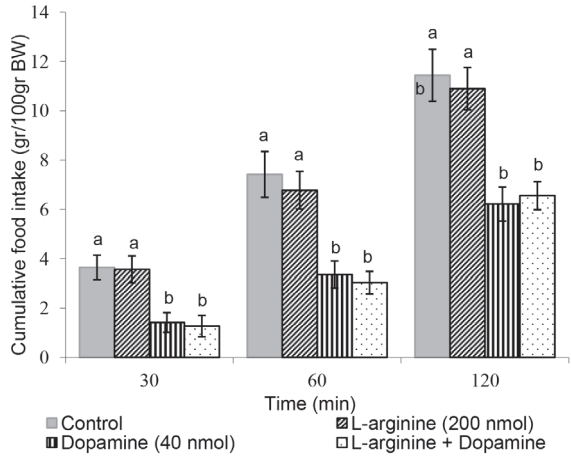

Figure 4. Effect of ICV injection of L-arginine (200 nmol), dopamine (40 pmol) and their combination on percent of metabolic cumulative food intake in neonatal layer type chickens. L-Arginine: nitric oxide precursor. There are significant differences between groups with different superscripts in a column (a and b; P<0.05)(treatment effect: F (3, 80) = 142.58, P<0.001; time effect: F (2, 80) = 127.1, P<0.001; treatment and time interaction: F (6, 80) = 4.12; P<0.001)

In Experiment 2, there was no significant effect on food intake after ICV administration of L-arginine (200 nmol) in layer-type chickens (P>0.05). Central injection of amphetamine (125 pmol) significantly decreased food intake compared to control group (P<0.001). Moreover, hypophagia induced by amphetamine significantly

amplified by L-arginine [treatment effect: $F(3, 80) = 57.13$, $P<0.001$; time effect: $F(2, 80) = 137.4$, $P<0.001$; treatment and time interaction: $F(6, 80) = 4.27$; $P<0.001$; Figure 2].

As shown in Figure 3, no significant effect was observed on percentage of food intake after ICV injection of L-NAME (100 nmol) in layer-type chickens. ICV injection of the DA (40 pmol) significantly diminished percentage of cumulative food intake in comparison to control group ($P<0.001$). Also, co-administration of L-NAME plus DA was not able to diminish DA induced hypophagia [treatment effect: $F(3, 80) = 96.24$, $P<0.001$; time effect: $F(2, 80) = 173.8$, $P<0.001$; treatment and time interaction: $F(6, 80) = 6.31$; $P<0.001$; Figure 3].

The ICV injection of L-arginine (200 nmol) had no significant effect on food intake compared to control group in layer-type chickens ($P>0.05$). Also, hypophagia was observed by central injection of DA (40 pmol) in birds ($P<0.001$). The co-administration of L-arginine and DA was not able to alter DA-induced hypophagia in layer-type chickens [treatment effect: $F(3, 80) = 142.58$, $P<0.001$; time effect: $F(2, 80) = 127.1$, $P<0.001$; treatment and time interaction: $F(6, 80) = 4.12$; $P<0.001$; Figure 4].

Discussion

To the best of our knowledge, the present study demonstrates for the first time probable interaction between central nitrergic and DAergic systems on food intake in neonatal chicken. It is well documented that NO is a central mediator of food intake in mammals (Morley and Flood, 1991) and birds (Choi et al., 1994). There are controversial reports on role of the NO on food intake. Central administration of L-NAME stimulates food intake in layer and broiler chicks (Khan et al., 2007). In this regard, our previous study showed that L-arginine (400 and 800 nmol) decreased food intake in neonatal layer type chicken while L-NAME (200 and 400 nmol) had a hypophagic effect (Alimohammadi et al., 2015; Hassanpour et al., 2015).

Studies on mammals revealed inconsistent results: ICV injection of L-NAME acts as an anorexigenic factor (De Luca et al., 1995) while L-arginine is considered an orexigenic factor (Morley and Flood, 1991). l-NNA, an inhibitor of the NO synthase, inhibited the food intake in broiler chickens (Choi et al., 1995); however, ICV injection of L-NAME had no effect on food intake in broilers (Khan et al., 2007). These controversial data might be the result of injection methods and species difference (Meade and Denbow, 2001). Additionally, it seems that genetic selection for meat or egg production has altered chicken brain neurological pathways associated with appetite regulation (Richards, 2003; Zendehdel et al., 2015 a). Layers have been selected for slow growth and low body weight while broilers have been genetically selected for rapid muscle and body weight gain. Broilers have higher feed consumption, basal metabolic rate and energy expenditure, possibly because of a genetically altered mechanism of food intake control (Denbow, 1994).

In this study, we used the sub-effective doses of the antagonists, which blocks the receptors, but without an effect on food intake, to examine possible interaction of

nitrergic and DAergic systems on food intake. The sub-effective dose of the antagonists had no adverse effect on appetite, sedation and even locomotion. The L-NAME effect was reversed by L-arginine but not through D-arginine. Likewise, L-lysine did not interfere with L-NAME effects (Calignano et al., 1993). We think that more studies are needed to investigate the effects of D-arginine and L-lysine on cumulative food intake in avian.

In this study, ICV injection of the DA (40 pmol) or amphetamine (125 pmol) significantly diminished food intake in layer-type chickens. In our previous study, we found ICV administration of L-DOPA or DA significantly decreased food intake in the FD_3 broilers (Zendehdel et al., 2014). On the contrary, injection of the DA had no effect on food intake in Leghorns and turkeys which were fed *ad libitum* (Denbow et al., 1983). Controversial reports may relate to inter- and between-strain differences and physiological status, which can influence food intake in response to neurotransmitters (Denbow et al., 1981).

In particular, ARC through its connections with other hypothalamic nuclei and brain regions regulates homeostatic food intake. Several limbic and cortical brain regions such as the nucleus accumbens (NAc), amygdala and hippocampus, orbitofrontal cortex (OFC) go forth using neurotransmitter systems such as DA, serotonin, opioids, NO and cannabinoids implicated in the rewarding effects of food (Salum et al., 2008; Volkow et al., 2011; Padovan-Neto et al., 2015; Zendehdel et al., 2015 b). It is reported that NO interact with other peptides on feeding behavior in the brain (Morley et al., 2011). However the direct mechanism for interaction of these two neurotransmitters is not fully elicited. It is clear that NO is involved in DA release and uptake (Antunes et al., 2005; Gomes et al., 2008). It is proposed that NO donors reduce the capacity of the DA transporter in a dose dependent manner. Direct synaptic contact was confirmed between the mesocortical and mesostriatal DA and NOS containing neurons. Also, it is proposed that an interaction exist between the NO and DA through a D_1-like receptor mechanism (Gomes et al., 2008). Our previous findings revealed the hypophagic effect of the DA regulates via D_1 receptors in chicken (Zendehdel et al., 2014).

The interaction between NO and DA neurons in the brain is complex. In this study the ICV injection of L-NAME diminished amphetamine (DA agonist)-induced hypophagia in birds. Dopaminergic neurotransmission is governed in part by the reuptake of extracellular DA via DA transporter which regulates the synaptic activity of DA into the pre-synaptic site (Salum et al., 2008). Psychostimulant drugs, predominantly amphetamine, act as a competitive inhibitor of the DA uptake. On the other hand, the interaction of the NO with DA transporter leads to increase in the velocity of the DA transport in the brain (Salum et al., 2008). Likewise, other mechanisms might include an effect of nitric oxide on DAergic neurotransmission. We think the interaction of the NO on monoamine transporters represents a new form of interneuronal interaction which needs much more investigation. According to our results there is an interaction between nitrergic and DAergic systems in layer-type chickens via a presynaptic pathway which by L-NAME (NO synthesis inhibitor) weakened the hypophagic effect of the amphetamine on food intake.

An interaction was reported between opioidergic and DAergic systems on food intake where β-endorphin and other opioid agonists increase DA release via D_1 receptors in the NAcc (Calignano et al., 1993; Toda et al., 2009). Recently, it has been proposed that a neural connection exists between nitrergic, DAergic and opioidergic system in the CNS where pretreatment with D_1 receptor antagonist diminished morphine-induced amnesia by L-arginine. Endogenous NO has a crucial role in modulation of effects of DA elicited by morphine (Toda et al., 2009). In human endometrial glandular epithelial cells, DA and morphine induced a transient surge of NO production (Tseng et al., 2000). The ARC and NAcc receive DAergic, serotonergic, opioidergic and nitrergic innervation from the upper parts of the brain (Padovan-Neto et al., 2015). nNOS interneurons of the NAcc receive afferents from the ventral tegmental area (VTA) and interact with the DAergic system (Hoque and West, 2012). For instance, ethanol withdrawal mechanism interacts via NO and DAergic systems in the NAcc in rat. In contrast, ICV injection of L-NAME significantly increased DA turnover in the ethanol withdrawal syndrome in mice (Uzbay and Oglesby, 2001). The NO plays key role in feeding behavior in the hypothalamus. It interacts with many feeding peptides such as ghrelin, NPY and orexin-A. For example, NPY-induced hyperphagia is blocked by NOS inhibitors in mice (Morley et al., 2011).

It has been known for decades that DA release in the ARC is associated with reward (Volkow et al., 2011). Striatal DA is critical for feeding, however, dopamine signaling can also inhibit food intake in the hypothalamus. There is an interconnection between hypothalamic NPY and DAergic system (Leal et al., 2013). The DA exerts complex pre- and post-synaptic connections on neuronal population involved in the control of energy expenditure and food intake (Conductier et al., 2011). Recently, Motahari et al. (2016) reported the possible mechanism of the NO in DA release. The NO donors increased DA release evoked by a range of different electrical stimulations (Hartung et al., 2011). The NO-mediated effects were independent of soluble guanylyl cyclase activation, DA transporters and Ca^{2+} activated K^+ channels. Furthermore, this frequency-dependent modulation of DA release by NO could be modulated via acetylcholine (ACh) (Motahari et al., 2016). Inhibition of nicotinic ACh receptors (nAChRs) in NA would prevent the effects of the NO on DA transmission. It seems the NO has 2 different mechanisms to control DA release (Hartung et al., 2011).

The second mechanism of the NO appears to be directly related to DA axons, and increases evoked DA regardless of the stimulus frequency. The NO increase the docking and fusion of DAergic vesicles and lead to increase in the DA release independent of frequency of stimulations (Motahari et al., 2016). It is possible L-arginine, combined with apomorphine or morphine, increases DA release in the NAcc and potentiates the induction of sensitization (Gholami et al., 2002). The effect of L-arginine, NOS inhibition by L-NAME significantly and dose-dependently decreases the acquisition of both apomorphine- and morphine-induced sensitization (Zarrindast et al., 2003). The injection of MK-801 (NMDA receptor antagonist) attenuates the development of opiate tolerance and dependence in rats (Motahari et al., 2016). So, the mechanism of NO action might relate to the changes in DA release in different rewarding areas of the brain (Motahari et al., 2016).

The NO stimulates adrenocorticotropin hormone and corticotropin-releasing factor (CRF) in the hypothalamus of the rat (Lee et al., 1999; Samarghandian et al., 2003). The CRF play crucial effects on energy intake and body weight regulation where known as hypophagic neurotransmitter (Zendehdel et al., 2016). ICV of the CRF into the VTA increased DA turnover in the NAcc (Risbrough et al., 2004). Additionally, DAergic system stimulates the CRF release in the paraventricular nucleus of the hypothalamus (Risbrough et al., 2004). Dopamine D_1 receptor antagonist (SCH 23390) decreases the startle enhancing effects of CRF (Meloni et al., 2006). However, in this study, we were not able to measure CRF levels after ICV injection of DAergic and NO drugs. Perhaps an interconnection might exist between the NO and DAergic systems on CRF neurons in food intake controlling centers of the brain. We think study is required to clarify the precise mechanism by which CRF, NO and DAergic systems affect food intake.

It seems that neural interaction exists between NO, DAergic and opioidergic system. There is considerable evidence behavioral changes induced by morphine are related to an increased turnover of the DA in the CNS. L-arginine enhanced morphine-induced changes in food intake and locomotion while ICV injection of the LNAME (NO synthase inhibitor) decreased both morphine-induced effects are sufficient evidence for suggesting NO is involved in the DAergic effects elicited by morphine (Calignano et al., 1993). The NO inhibitors (myricitrin) blocked the behavioral effects of apomorphine via protein kinase C (PKC) (Pereira et al., 2011). Supporting the proposed involvement of nitrergic mechanisms in myricitrin induced inhibition of apomorphine-induced stereotypy, tamoxifen, a PKC inhibitor, also inhibited this behavior, indicating the PKC inhibition also exerts an antipsychotic-like effect (Pereira et al., 2011). Perhaps, the observed results on mediatory role of the NO and DAergic systems on feeding behavior happen via PKC pathway. However, further molecular studies are needed to clarify the obtained results.

Most research on feeding behavior regulatory mechanisms was performed with rat models, whereas few investigations were done in birds. Actually, there was no similar research to compare our results on mediatory role of the NO in DA release as poultry model. So, based on findings, there might be an interaction between central nitrergic and DAergic systems on food intake in layer-type chicken. D_1-like receptor stimulation by a D_1 not D_2 agonist increases postsynaptic current which presynaptic D_1-like receptors potentiate spontaneous neurotransmitter release (Conductier et al., 2011). These results imply a presynaptic mechanism might exist between two systems. The authors recommend the new finding of the current study can used as base information on the regulatory role of NO on the hypophagic effect of the DA in birds. Further research is required to clarify any direct interaction of cellular and molecular signaling pathways in the interconnection between nitrergic and DAergic systems on feeding behavior in avian.

Conflict of interest

There is no conflict of interest.

Human and Animal Rights

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

Informed Consent

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

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