Dopamine- induced hypophagia is mediated via NMDA and mGlu1 receptors in chicken

Taheriyan, M.R., Baghbanzadeh, A.*, Zendehdel, M.

Department of Basic Sciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

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Correspondence
Baghbanzadeh, A.
Department of Basic Sciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
Tel: +98(21) 61117081
Fax: +98(21) 66933222
Email: abaghban@ut.ac.ir

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Abstract:

BACKGROUND: Feeding behavior is regulated by a complex network which interacts via diverse signals from central and peripheral tissues. It is known dopaminergic and glutamatergic systems have crucial role on food intake regulation but scarce reports exist on their interaction in appetite regulation in broilers. **OBJECTIVES:** The present study was designed to examine the role of glutamatergic system on dopamine-induced hypophagia in neonatal meat-type chicken. **METHODS:** In experiment 1, chicks received ICV injection of control solution, dopamine (40 nmol), MK-801 (NMDA glutamate receptors antagonist, 15 nmol) and co-injection of dopamine + MK-801. In experiment 2, birds were ICV injected with saline, dopamine (40 nmol), CNQX (AMPA glutamate receptors antagonist, 390 nmol) and co-injection of dopamine + CNQX. In experiment 3, chicks received ICV injection of control solution, dopamine (40 nmol), AIDA (mGLUR1 glutamate receptors antagonist, 2 nmol), dopamine + AIDA. Experiments 4 and 5 were similar to experiment 3, except birds were injected with LY341495 (mGLUR2 glutamate receptors antagonist, 150 nmol) and UBP1112 (mGLUR3 glutamate receptors antagonist, 2 nmol) instead of AIDA. Then the cumulative food intake was measured until 120 min post injection. **RESULTS:** According to the results, ICV injection of dopamine significantly decreased food intake ($p<0.001$). Co-injection of dopamine and MK-801 decreased dopamine induced hypophagia ($p<0.001$). Moreover, the food intake of chicks was significantly increased by co-injection of AIDA and dopamine ($p<0.001$). **CONCLUSIONS:** These results suggest dopamine-induced hypophagia is mediated via NMDA and mGlu1 receptors in chicken.

Introduction

Appetite is modulated by complex neurochemical pathways in different parts of the brain, such as the striatum, hypothalamus and amygdala. To date frequent neuropeptides and neurotransmitters in the brain have been discovered that regulate food intake (Boswell, 2005). Dopamine (DA) is one of the main neurotransmitters in the brain and regulates several physiological functions such as motion, motivation, novelty, memory and reward (Ladepeche et al., 2013).

Dopaminergic (DAergic) system plays a crucial role on appetite regulation in both mammalian and avian. For instance, D1 and

D2 agonist diminish food intake in rats (Volkow et al., 2011). DA-induced hypophagia mediates by D1 receptors in chicken while other receptors (D2, D3 and D4) may have no role in appetite regulation (Zendehdel et al., 2014b). It is well documented that central feeding behavior is not regulated via a single neuropeptide and a wide distributed neural network interacts with a diversity of neurotransmitters on feeding status (Irwin et al., 2008).

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS) and plays a role in reward in the different reward and hypothalamic centers (McFadden et al., 2014). Glutamate receptors are classified into two groups, based on their pharmacology and mechanism. The ionotropic receptors including inotropic include N-methyl-D-aspartate (NMDA), Kainate, AMPA receptors and the metabotropic receptors (mGluRs) with different subtypes (Charles et al., 2014). It is reported that of the lateral hypothalamic AMPA receptors, glutamate ionotropic receptors induced feeding in rats (Hettes et al., 2010). In addition, injection of NMDA and AMPA-kainite receptor antagonists into ventral striatal and ventral pallidal areas of the pigeon induced food intake (Da Silva et al., 2003). Also, the ICV injection of DL-AP5 (NMDA receptor antagonist) increased food consumption in FD3 broiler dose dependently (Taati et al., 2011).

A relation between central DA and Glutaminergic systems has been reported. It is reported that dopamine D1 receptor interacts with NMDA mediated signaling in NMDAR-mediated signaling and working memory in the CNS (Ladepeche et al., 2013). For instance, D1 and NMDA receptors interact on the Volitional consumption of ethanol in rats (McMillen et al., 2013) while, blockade of D1 receptors had no changes in the dynamics of glutamate release, blockade of D2 receptors increased glutamate levels during food consumption in rat (Mikhailova et al., 2003).

Despite numerous investigations about the role of neurotransmitters on ingestion, different aspects of appetite regulation in poultry are unclear (Denbow, 1994).There is evidence that central mechanisms for food intake regulation are different between mammalian and birds (Zendehdel and Hassanpour 2014a). So, it will be useful to study the regulatory mechanisms of neurotransmitters in feeding behavior in birds (Furuse, 2002, Zendehdel and Hassanpour 2014b). To the best of our knowledge, no report exists on the role of glutamatergic system on DA-induced hypophagia in domestic fowls. Hence, this study was to determine the possible involvement of the glutamatergic system on DA-induced hypophagia in neonatal meat-type chicken.

Materials and Methods

Animals: In this study, a total of 240 one-day-old broiler chickens (Ross 308) were purchased from local hatchery (Mahan Co. Iran). Birds were kept as flocks for 2 and then randomly transferred into individual cages at a temperature of 30 ± 1ºC with 50 ± 2 percent humidity (Olanrewaju et al., 2006). A commercial diet was provided during the study containing 21 % crude protein and 2850 kcal/kg of metabolizable energy (Chineh Co. Iran). All birds received food and fresh water ad libitum during the study. Just 3 h prior to ICV injections, chicken were food deprived (FD3) though they had free access to water. The injections were applied to all birds 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 Institutional Ethical Committee of the Iranian government for animal care.

Experimental drugs: Drugs including dopamine, MK-801 (NMDA glutamate receptors antagonist), CNQX (AMPA glutamate receptors antagonist), AIDA (mGLUR1 glutamate receptors antagonist), LY341495 (mGLUR2

glutamate receptors antagonist), UBP1112 (mGLUR3 glutamate receptors antagonist) and Evans blue were purchased from Sigma Co. (Sigma, USA) and Tocris Co. (UK). Drugs were first dissolved in absolute dimethyl sulfoxide (0.08% DMSO) then diluted with 0.85% saline containing Evans blue at a ratio of 1/250. DMSO with this ratio does not have cytotoxic effect (Blevins et al., 2002; Qi et al., 2008).

ICV injection procedures: In this study, 5 experiments were designed to investigate interconnection of DAergic and glutamatergic systems on cumulative food intake in neonatal broiler birds (each experiment includes 4 groups with 3 replicates (n=12). Prior to each experiment, the chicks were weighed and based on their body weight divided into experimental groups so the average weight between treatment groups was as uniform as possible. ICV injection was applied using a microsyringe (Hamilton, Switzerland) without anesthesia according to the technique previously described by Davis et al., (1979) and Furuse et al., (1997). Briefly, the head of the birds was held by acrylic device, the bill holder was 45º and calvarium parallel to the surface of table (Van Tienhoven and Juhasz, 1962). A hole was drilled in acrylic device over the right lateral ventricle of the skull. A microsyringe was inserted into the right ventricle via the hole and tip of the needle penetrated 4 mm beneath the skin of the skull. It is shown that, there is no injection-induced physiological stress using this method in neonatal chicks (Saito et al., 2005). Each chick received a 10 µl ICV injection of vehicle or drug (Furuse et al., 1999). There was no increased intracranial pressure using ICV injections of 2, 5 and 10 µl of saline or solution (Furuse et al., 1999). The control group received control solution (saline containing Evan's blue 10 µl) (Furuse et al., 1999). Right away after injection, FD3 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 after 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 was used just once in each experimental group. At the end of the experiments, accuracy of placement of the injection in the ventricle was verified by presence of Evans blue followed by slicing the frozen brain tissue. In each group, 12 birds received injection, but just data of those individuals where dye was present in their lateral ventricle (9-12 chickens per group) were used for analysis. All experimental procedures were done from 8:00 A.M. until 3:30 P.M (Jonaidi and Noori, 2012; Zendehdel and Hassanpour 2014; Hassanpour et al., 2015).

Feeding experiments: In experiment 1, four groups of FD3 chicks received a dose of either the ICV injection of A: control solution (saline containing Evan's blue), B: dopamine (40 nmol), C: MK-801 (NMDA glutamate receptors antagonist, 15 nmol), D: combination of dopamine + MK-801. In experiment 2, group A: ICV injected with saline, B: dopamine (40 nmol), C: CNQX (AMPA glutamate receptors antagonist, 390 nmol), D: combination of dopamine + CNQX. In experiment 3, FD3 chicks received ICV injection of control solution (A), dopamine (40 nmol), AIDA (mGLUR1 glutamate receptors antagonist, 2 nmol), D: dopamine + AIDA. In experiment 4, group A: ICV injected with saline, B: dopamine (40 nmol), C: LY341495 (mGLUR2 glutamate receptors antagonist, 150 nmol), D: dopamine + LY341495. In experiment 5, group A: ICV injected with saline, B: dopamine (40 nmol), C: UBP1112 (mGLUR3 glutamate receptors antagonist, 2 nmol), D: dopamine + UBP1112. Each bird was injected once only. The injection procedure is described in Table 1. These doses of drugs were determined according to the previous (Zeni et al., 2000; Antunes et al., 2005; Baghbanzadeh and Babapour, 2007 Zendehdel et al., 2009, 2012, 2014a).

Statistical analysis: Data were presented

as mean ± SEM (standard error of the mean). 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). For treatment showing a main effect by ANOVA, means were compared by Tukey-Kramer test. P<0.001 was considered as significant difference between treatments.

Results

Effects and interactions of central DAergic and glutamatergic systems on cumulative food intake in FD3 neonatal meat-type chicks are shown in Figs. 1-5.

In this study to examine the possible interaction between these two systems, effective and sub-effective doses of their antagonists were administered to confront nullifying effects of the agents. In other words, for interactions the effective dose antagonists were injected with the sub-effective dose of the antagonist of the other system. According to the results, ICV injection of an effective dose of DA (40 nmol) significantly decreased cumulative food intake in FD3 compared to control group (p<0.001) (Figs 1-5).

In experiment 1, ICV injection of sub effective dose of the NMDA glutamate antagonist (MK-801, 15 nmol) had no significant effect on food intake in FD3 birds (p>0.05) while co-injection of dopamine and MK-801 attenuated DA-induced hypophagia (p<0.001).

In experiment 2, ICV injection 390 nmol of CNQX (AMPA glutamate antagonist) had no effect on feeding behavior in FD3 neonatal meat-type chicken (p>0.05). Also, co-administration of CNQX + DA had no effect on DA-induced hypophagia in FD3 neonatal meat-type chicken (p>0.05).

In experiment 3, no significant effect was observed on food intake after ICV administration of AIDA (mGLUR1 glutamate antagonist, 2 nmol) in FD3 neonatal meat-type chicken

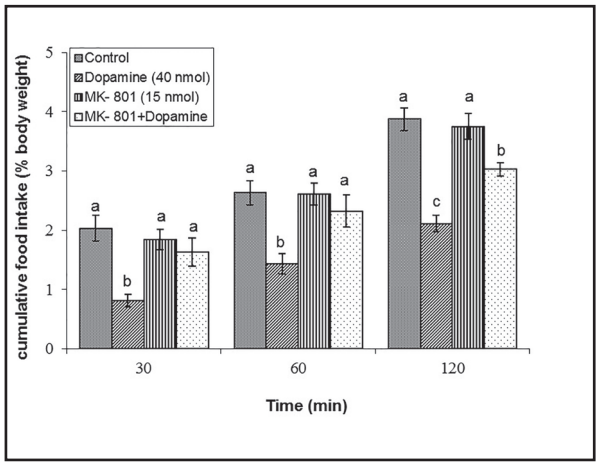

Figure 1. Effects of intracerebroventricular injection of control solution, dopamine, MK-801 and a combination of dopamine plus MK-801 on cumulative food intake (% BW) in neonatal chicks. MK-801: NMDA glutamate receptors antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time(p<0.001).

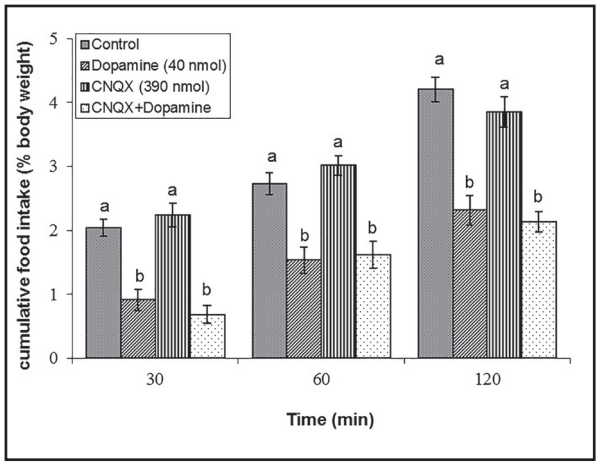

Figure 2. Effects of intracerebroventricular injection of control solution, dopamine, CNQX and a combination of dopamine plus CNQX on cumulative food intake (% BW) in neonatal chicks. CNQX: AMPA glutamate receptors antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.001).

(p>0.05) but, DA-induced hypophagia significantly attenuated by co-injection of DA and AIDA (p<0.001).

In experiment 4, ICV injection of (mGLUR2 glutamate antagonist, 150 nmol) was not able to impress significant change on appetite regulation in birds (p>0.05). Also, combination of DA and LY341495 was not able to decrease

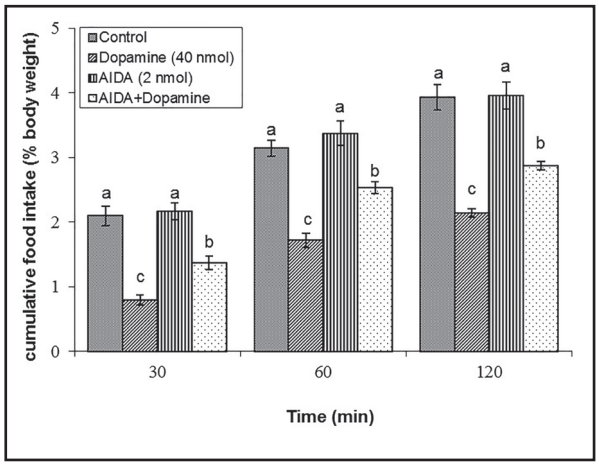

Figure 3. Effects of intracerebroventricular injection of control solution, dopamine, AIDA and a combination of dopamine plus AIDA on cumulative food intake (% BW) in neonatal chicks. AIDA: mGLUR1 glutamate receptors antagonist. Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments at each time ($p<0.001$).

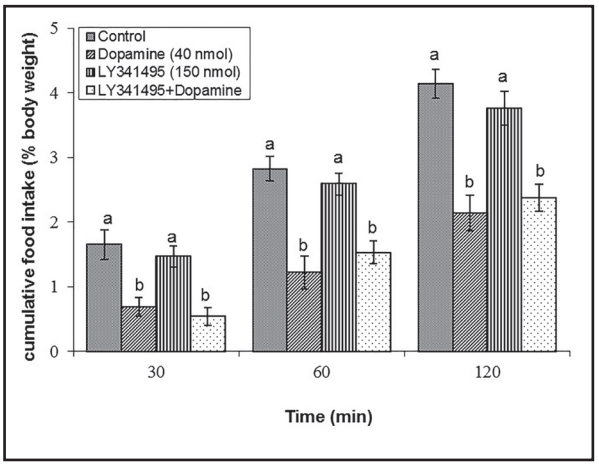

Figure 4. Effects of intracerebroventricular injection of control solution, dopamine, LY341495 and a combination of dopamine plus LY341495 on cumulative food intake (% BW) in neonatal chicks. LY341495: mGLUR2 glutamate receptors antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p<0.001$).

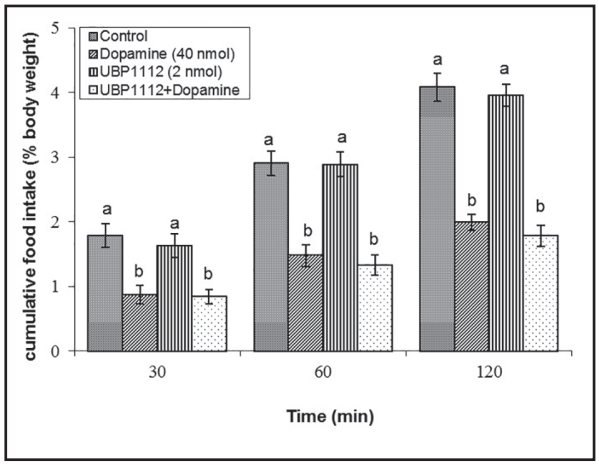

Figure 5. Effects of intracerebroventricular injection of control solution, dopamine, UBP1112 and a combination of dopamine plus UBP1112 on cumulative food intake (% BW) in neonatal chicks. UBP1112: mGLUR3 glutamate receptors antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p<0.001$).

the hypophagic effect of DA in FD3 neonatal meat-type chicks in comparison to control group ($p>0.05$).

In experiment 5, ICV of DA significantly decreased feeding behavior ($p<0.001$) and injection of UBP1112 (mGLUR3 glutamate antagonist, 2 nmol) had no effect on cummulative food intake in meat-type chicks ($p>0.05$). Co-injection of DA + UBP1112 was not able to diminish DA-induced hypophagia in FD3 neonatal meat-type chicks compared to control group ($p>0.05$).

Discussion

To the best of our knowledge, this is the first report on interactions between DAergic and glutamatergic systems on neonatal broiler feed intake. According to the results (Figs. 1, 2, 3, 4 and 5), ICV injection of the DA significantly decreased food intake in FD3 neonatal meat-type chicken. A daily decrease on cumulative food intake was reported using D1 (SKF 38393) and D2 (apomorphine) agonists in rats (Kuo Dy et al., 2002). A dose dependent decrease in food intake was detected using D1 agonist (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 reported the ICV injection of the DA decreased food intake in broiler chickens (Zendehdel et al., 2014a).

As observed from the results, co-injection of dopamine and MK-801 (NMDA glutamate antagonist) decreased dopamine induced hy-

pophagia in FD3 neonatal meat-type chicken (Fig. 1). The glutamatergic and the DAergic system plays key role in several brain functions, such as motion and reward. Over the past decades several researches have been done to discover the direct mechanism responsible for the central DA and glutaminergic systems interaction. Release of the DA activates postsynaptic membrane DA1/5 receptors which can affect NMDA receptors signaling in striatal and hippocampal neurons in the rat (Ladepeche et al., 2013). High concentrations of glutamate receptors in the food regulation regions of the brain have a significant effect on DA release (McFadden et al., 2014). Lateral hypothalamic injection of ionotropic glutamate receptors amplifies feeding while NMDA receptor antagonist suppresses natural feeding (Stanley et al., 1996).

There is little information about interaction of DA and glutamatergic systems in the brain. DAergic neurons can be protected against neurotoxic levels of amphetamines via NMDA receptor antagonist, MK-801(McMillen et al., 2013). It is suggested that D1 receptor agonist activate DARPP-32 through the cAMP/PKA pathway while NMDA agonist blockade this effect via increasing the intracellular Ca2+ and activation of calcineurin (McMillen et al., 2013). Based on the literature they were not able to investigate interaction of other neurotransmitters with DA-glutamatergic on food intake regulation. We think merit researches needed to determine a direct cellular and molecular mechanism for interaction of DA-glutamatergic systems on feeding behavior.

Herein, food intake increased by co-injection of AIDA (mGLUR1 glutamate antagonist) and dopamine in FD3 neonatal meat-type chicken (Fig. 3). In this regard, it was reported that food consumption elicits via lateral hypothalamic mGluR1 and/or mGluR5 in rat (Charles et al., 2014). Stimulation of food consumption followed by reduction of elicited feeding using mGluR1 and mGluR5 antagonists, suggests feeding behavior is mediated by mGluRs, specifically the R1 and R5 subtypes (Charles et al., 2014). There are interesting reports on indirect involvement and mediatory role of the ionotropic receptors on mGluRs-induced feeding. For example, activation of mGluR5 can modify NMDA synaptic currents within lateral hypothalamus melanin-concentrating hormone (MCH) neurons (Charles et al., 2014). As seen from the Fig.1 vs. Fig.3, NMDA antagonists strongly minimized DA-induced hypophagia (Fig.1) while mGluR1 antagonist had partial effect (Fig.3). In this study, there was no interaction between DA and other mGluRs (mGLUR2 and mGLUR3).

There is limited information about involvement of mGluRs with DAergic system on feeding behavior. Although there was a difference in central regulation in feeding behavior between broilers and layer chicken, no report was found on interaction of these systems in layer-type chicken. In our previous study, we found that mGLUR2 and mGLUR3 receptors had no effect on the 5-HT induced hypophagia in FD3 chickens (Seyedali Mortezaei et al., 2013). It seems that metabotropic receptors have partial interaction with other neurotransmitters in food intake regulation in broilers. The mGluR1 mechanically acts via phospholipase C activation which leads to the formation of IP3 and diacylglycerol, intracellular release of Ca2+ and stimulation of protein kinase C, while mGLUR2 and mGLUR3 receptors coupled to adenylyl cyclase and cyclase respectively. Different subtypes in each mGluR group have different functional roles. We think the observed differences might relate to the different cellular mechanism of actions of the mGLURs. However, merit studies need to determine direct cellular and molecular interaction of mGLURs with other neurotransmitters.

However, the role of DA in feeding behaviors is complex and varies by brain region. Perhaps DA-glutamatergic system interaction on food intake mediates via other neurotransmitters

such as GABA (Richard and Berridge, 2011), orexin and neuropeptide Y (NPY) (Charles et al., 2014) and opioids (Madhavan et al., 2013). For example, pre-treatment with nicotine decreased the NMDA-induced dopamine release from nucleus accumbens nerve terminals (Salamone et al., 2014). Because of the limitation of this study, we were not able to investigate interaction of other neurotransmitters with DA-glutamatergic on food intake regulation. To our knowledge, there has been no previous study on the role of central DAergic and glutamatergic systems on food intake in avian. So, we were not able to compare our results with it. Most research on central food intake regulation has been done with rat models, whereas few investigations have been done on birds. These observations can be used as base information on central food intake regulation in birds. Finally, the authors recommend further merit investigations be done to clarify direct cellular and molecular signaling pathways of the DAergic and glutamatergic systems with other receptors in physiology of food intake regulation in poultry.

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میانجیگری گیرنده‌های NMDA و متابوتروپیک نوع ۱ گلوتامات بر کاهش اخذ غذای القا شده با دوپامین در جوجه

محمدرضا طاهریان علی باغبان‌زاده* مرتضی زنده‌دل

گروه علوم پایه، دانشکده دامپزشکی دانشگاه تهران، تهران، ایران

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چکیده

زمینه مطالعه: رفتار تغذیه‌ای از راه مسیرهای پیچیده بواسطه سیگنال‌های مرکزی و اندام‌های محیطی تنظیم می‌شود. مشخص شده است که سیستم دوپامینرژیک و گلوتاماترژیک نقش مهمی در تنظیم مصرف خوراک دارند اما گزارشات کمی در مورد تقابل عمل آنها در پرندگان وجود دارد. **هدف:** این مطالعه به‌منظور بررسی نقش سیستم گلوتاماترژیک بر کاهش اشتهای ناشی از دوپامین در جوجه‌های گوشتی یک روزه طراحی شد. **روش کار:** در آزمایش اول جوجه‌ها تزریق داخل بطنی مغزی محلول کنترل، دوپامین (۴nmol)، MK-۸۰۱ (آنتاگونیست گیرنده NMDA گلوتاماتی، ۱۵nmol) و تزریق توام دوپامین + MK-۸۰۱ را دریافت کردند. در آزمایش دوم جوجه‌ها با محلول کنترل، دوپامین (۴nmol)، CNQX (آنتاگونیست گیرنده AMPA گلوتاماتی، ۳۹۰nmol) و استفاده توام دوپامین + AMPA تزریق داخل بطنی مغزی شدند. در آزمایش سوم جوجه‌ها تزریق داخل بطنی مغزی محلول کنترل، دوپامین (۴nmol)، AIDA (آنتاگونیست گیرنده mGLUR۱ گلوتاماتی، ۲nmol) و دوپامین + AIDA را دریافت کردند. آزمایش ۴ و ۵ مشابه آزمایش ۳ بود بطوری‌که جوجه‌ها LY۳۴۱۴۹۵ (آنتاگونیست گیرنده mGLUR۲ گلوتاماتی، ۱۵۰nmol) و UBP۱۱۱۲ (آنتاگونیست گیرنده mGLUR۳ گلوتاماتی، ۲nmol) را بجای AIDA دریافت کردند. سپس مصرف تجمعی خوراک تا ۱۲۰ دقیقه پس از تزریق اندازه‌گیری شد. **نتایج:** با توجه به نتایج بدست آمده تزریق داخل بطنی مغزی دوپامین بطور معنی‌داری موجب کاهش اخذ غذا شـد ($p<۰/۰۰۱$). تزریق توام دوپامین و MK-۸۰۱ موجب کاهش اثرات ضد اشـتهایی دوپامین شد ($p<۰/۰۰۱$). مصرف خوراک در جوجه‌ها بواسطه تزریق توام دوپامین و AIDA افزایش یافت ($p<۰/۰۰۱$). **نتیجه‌گیری نهایی:** نتایج نشان‌دهنده این بود که کاهش اشتهای ناشی از دوپامین از طریق گیرنده‌های NMDA و mGLUR۱ گلوتاماترژیک در جوجه‌های گوشتی میانجی‌گری می‌شود.

واژه‌های کلیدی: جوجه، دوپامین، اخذ غذا، گلوتامات

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*) نویسنده مسؤول: تلفن: ۶۱۱۱۷۰۸۱ (۲۱)۹۸+ نمابر: ۶۶۹۳۳۲۲۲ (۲۱)۹۸+ Email: abaghban@ut.ac.ir