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ORIGINAL ARTICLE

Survey the interference of Glutamate – Histamine in Central Nervous System in food intake at broiler chickens: (A Physiological Approach to Neuro-Endocrinal system in poultry)

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ABSTRACT

Glutamate and histamine are two inhibitory factors of appetite in central nervous system of birds. In the present study, interference effect of glutamate-histamine was evaluated. The broiler weighing 700±50gr, implanted sterile canule in right ventricle of their brine, were used. Animals were fasted for 24 hours before intra-ventricular micro-injection. After canule-implantation the birds were divided to different groups in terms of kind of injection drugs. Each group included 8 broilers and one group was considered as control. Glutamate, histamine, histamine antagonist and glutamate-histamine solutions were injected to right ventricle of brain and then the amount of food intake in all groups in minutes 15, 30,45,60,90,120,180 and 240 after injection was measured. Results showed that intra-ventricular injection of glutamate, histamine and histamine-glutamate caused statistically considerable decrease in food intake compared to control groups (P<0.05), whereas histamine antagonist induced significant increase in food intake in comparison to control group in all times (P<0.05).In minutes 30,45,60,120 and 180,appetite in glutamate-histamine was less than group glutamate but finally in minute 240 there was not seen any significant difference between two groups. In conclusion, it seemed the inhibitory effect of histamine on glutamate receptors prevented the intensive effect of contemporarily injection of these two drugs.

Key words: *Appetite, Glutamate, Histamine, Broiler*

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INTRODUCTION

Food intake regulation in birds represents a complex homeostatic mechanism involving multiple levels of control. A considerable number of neurotransmitters have also been shown to either increase or decrease food intake when injected directly into the central nervous system. Genetic selection, physiological state of the bird, and the site of injection influence the response to these compounds. When injected into the brain, neuropeptide Y, avian pancreatic polypeptide, and opioids are potent stimulators of food intake whereas other peptides investigated to date decrease food intake. L-glutamic acid is the major excitatory neurotransmitter in the central nervous system (CNS) [1, 2], probably involved in normal brain activities as well as CNS developmental processes including cell migration, differentiation and death [2]. Many neurons, and even glial cells, bear glutamate receptors (GluR) on their plasma membrane [2]. Glutamate is the most abundant amino acid in the mammalian and avian brain, a part of which is located in the extracellular fluid (ECF). Glutamate serves as an important potential fuel reserve. The oxidation of glutamate to oxaloacetate yields 12 ATP per molecule of glutamate. Therefore, when the brain has insufficient glucose concentrations or glycolytic flux is reduced, the brain mobilizes glutamate as a fuel [3]. In this regard, the energy available from glutamate is similar to glucose as a fuel reserve. Systemic, ICV or local injections of glutamate or its agonists into the lateral hypothalamus elicits a dose-dependent stimulation of feed intake in mammals [4, 5]. Meanwhile, systemic, ICV or local injections of some GluR antagonists into the median raphe nucleus[6], accumbence nucleus [4,7] and ventral striatal and ventral pallidal areas [8] increases feed intake. These findings suggest that several central and peripheral glutamatergic circuits are involved in feed intake regulation. Although glutamate receptors are widely distributed in the avian brain, there is little information on the impact of glutamate and GluRs on feeding

behavior in the domestic fowl [9, 10]. In the CNS, histamine is a putative neurotransmitter that is heterogeneously distributed in the brain and synthesized from the amino acid precursor histidine, which is then decarboxylated to histamine via histidine decarboxylase [11]. Several lines of evidence also suggest that central histamine may be involved in the regulation of feeding behavior. Intracerebroventricular injection of HA suppresses food intake in rats[12], goats [13] and chickens [14]. Exogenous histamine has been shown to decrease food intake when injected into the brain of broiler chickens [14, 15]. The aim of present study to evaluate the synchronic interference of Glutamate and Histamine in Central Nervous System in food appetite of broilers.

MATERIAL AND METHODS

Animals

The male one-day old chickens Ross strains were purchased and maintained for 3 weeks in a flock shape, under standardized situation of husbandry .Water and food were supplied adlibitum. Then in third weeks age of them after induction of anesthesia under a sterilized surgery were implanted a canula in lateral ventricle of their brain. After canula implantation for evaluation of normal condition of birds, they were maintained in a rest for 5 days. Then the birds were divided in to 6 groups, each consisting 8 birds. After injection of considered quantities of drugs to brain of ventricle, the amount of food intake in different time periods including 15, 30, 45, 60, 90,120,180 and 240 minutes were measured. The study groups comprised: 1.serum physiology 2.Histamine 3.Histamine Antagonist(Ahis) 4. Histamine Antagonist(Ahis)+Glutamate 6.Histamine+Glutamate.

The method of Maintenance of Chickens

The chickens were maintained under temperature of 30 to31 ^{0}C in the first 3 days ,then the temperature was decreased 1 degree of centigrade for each day and from day 12 was fixed in 22 ^{0}C. Relative humidity was %40 and light period was 24 hours. The diet of chickens was cramble starter (number21) that was supplied through the whole period of study to chickens. The rate of protein of diet was %21.5 and the energy amount was estimated 2950 Kkal/kg.

Drugs

Drugs used in the present study included Histamine(Sigma-USA), *Chlorophenylamine as Histamine antagonist*(Sigma-USA),Glutamate(Glutamic acid)(Tocris-USA) and Serum physiology(%0.9 Sodium Chloride solution)(Drug and injections production company of Iran).All drugs were dissolved in sterile normal saline 30 minutes before microinjection to right ventricle of brain.

Surgical Procedure

To deliver the compounds to be tested ,firstly we found the place of bragma, confluence region of frontal and parietal bone and then cannula implantation was carried out by 29-gauge guide cannula in coordinate as AP:6.7 mm L:0.7 mm and depth:3.75 (figure.1and 2).The canullas were then fixed to the scull using three screws and dental acrylic (Marlic medical industries company).At least ,10 days were allowed for recovery from the surgery.

Intraventricular microinjection

Intraventricular microinjection of normal saline (control), glutamate, histamine, *Chlorophenylamine (as histamine antagonist)* was performed by23-gauge syringe gauge. The volume of the drug solution to be injected into right-lateral ventricle was 5 μL, and the injection was slowly made over a period of 1 min.

Cannula verification

At the end of each experiment, 0.25 μL metylene blue was injected into the lateral ventricle of brain. The animals were euthanized with high dose ether, and perfused intracardially with physiological saline followed by 10 % formalin solution. Brains were removed and placed in the formalin (10 %) solution. At least 3 days later, the brains were sectioned coronally (50-100 μm), and viewed under a loupe to localize the injection site. (Fig.3)

Statistical analysis

To evaluate significance differences among every group, one-way analysis of variance (ANOVA) and Duncan s test were applied. In figures, all values are expressed as the mean ± SEM. A value of $P < 0.05$ was considered statistically significant.

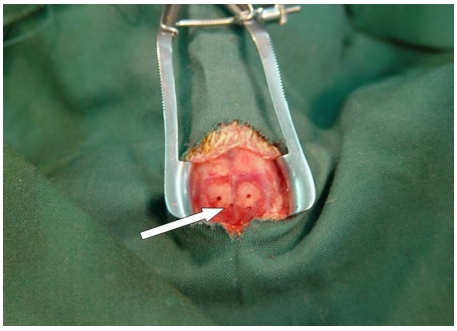

Fig1.Arrow represents the place of cannula implantation in to right lateral ventricle.

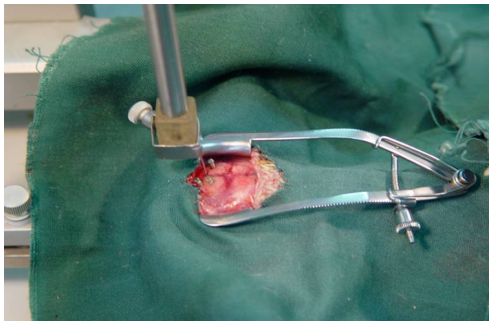

Fig2.The stage of cannula implantation

Fig3.Represented ventricles of broiler brain filled with metylene blue for Cannula verification

RESULTS

15, 30 and 45minutes after injection

Histamine antagonist group was higher than all groups in respect of food intake statistically (P<0.05).Groups Glutamate and Glutamate+ Histamine, Histamine and Ahis+Glu were lower compared to control in food intake statistically (P<0.05) (Fig4, 5 and6).

60 and 90 minutes after injection

The results showed a statistically considerable difference between all groups (P<0.05).all earlier results between groups repeated in these time, in other words Histamine Antagonist induce significant increase in food intake compared to control(P<0.05) and food intake in all other groups was statistically lower than control(P<0.05)(Fig 7)

120 minutes after injection

Similarly food consumption in group Histamine Antagonist was higher than all groups ,and other groups were lower in food intake(P<0.05).and also there was not statistically difference between Ahis+Glu and His+Glu groups.appetite in group injectioned Histamine was higher than Group Glu and group Glu was higher than Ahis+Glu and His+Glu groupsin food intake (P<0.05)(Fig 8)

180 and 240 minutes after injection

Group Histamine Antagonist was higher than all group in food consumption. Appetite in Groups Glu andHis were higher than Ahis+Glu and His+Glu groups and also in group His+Glu was higher than Ahis+Glu group(Fig 9 and10)

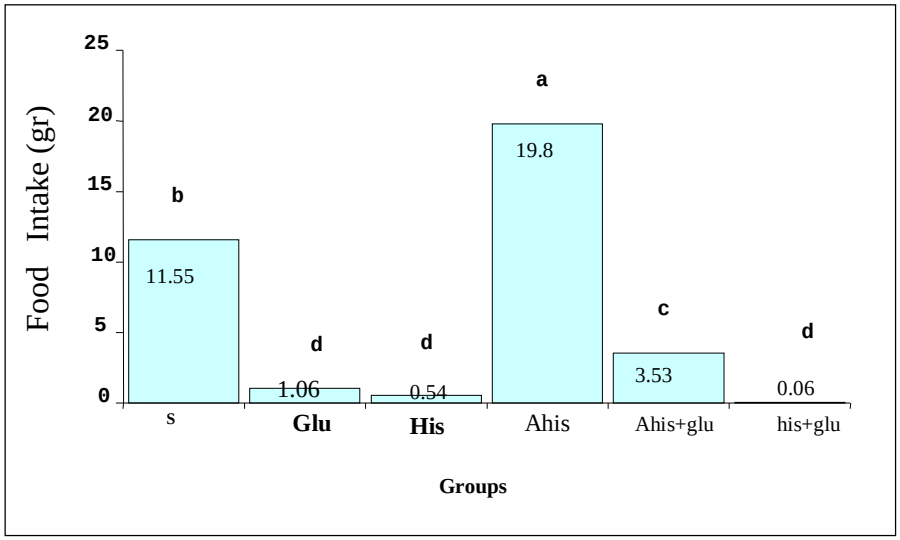

Fig4.Food Intake (gr) in 15 min after intraventricular injection S=serum physiology,His= Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05)

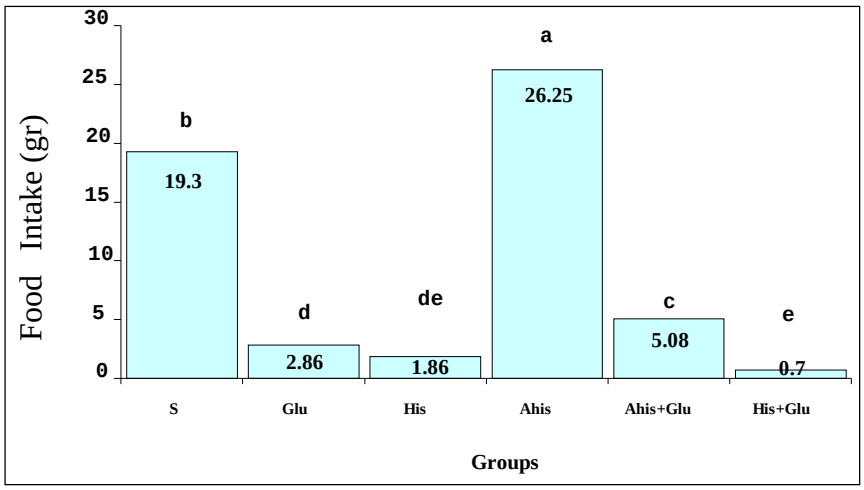

Fig5.Food Intake (gr) in 30 min after intraventricular injection S=serum physiology,His=Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05)

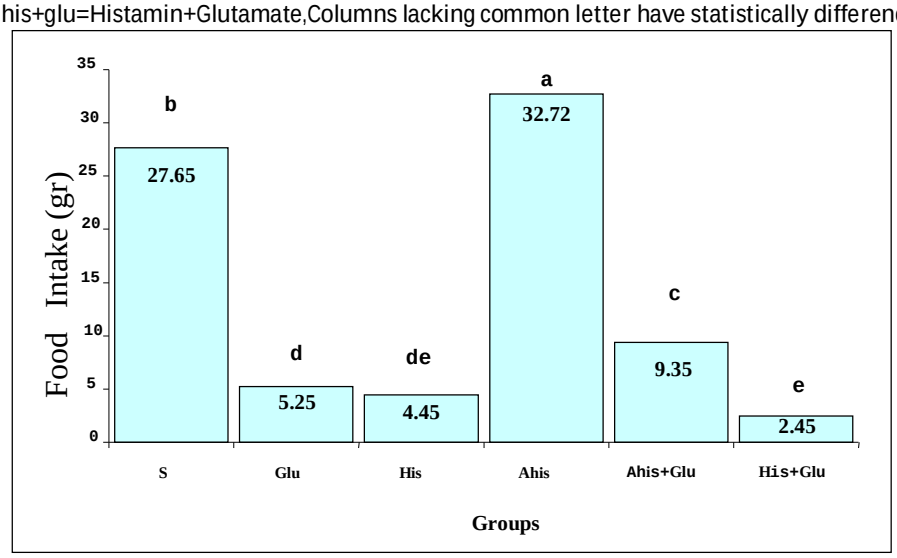

Fig6.Food Intake (gr) in 45 min after intraventricular injection S=serum physiology,His=Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05)

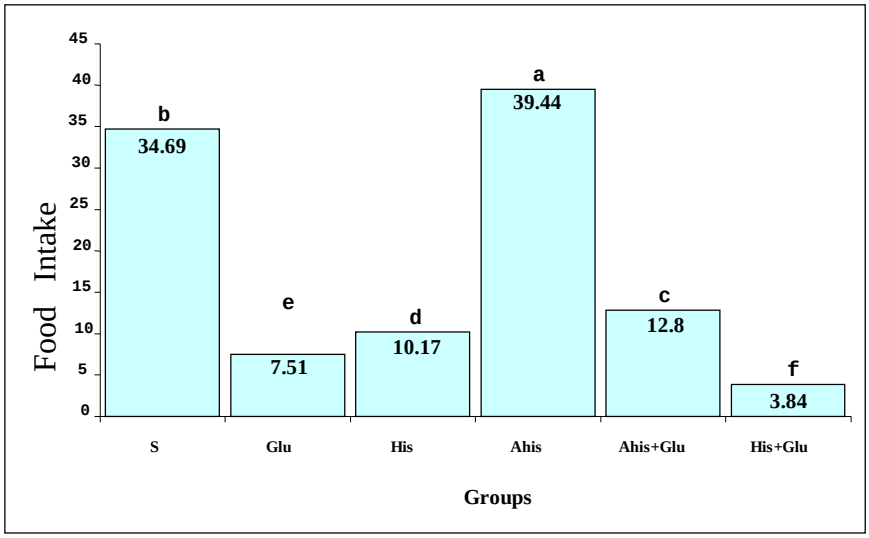

Fig7.Food Intake (gr) in 60min after intraventricular injection S=serum physiology,His=Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05)

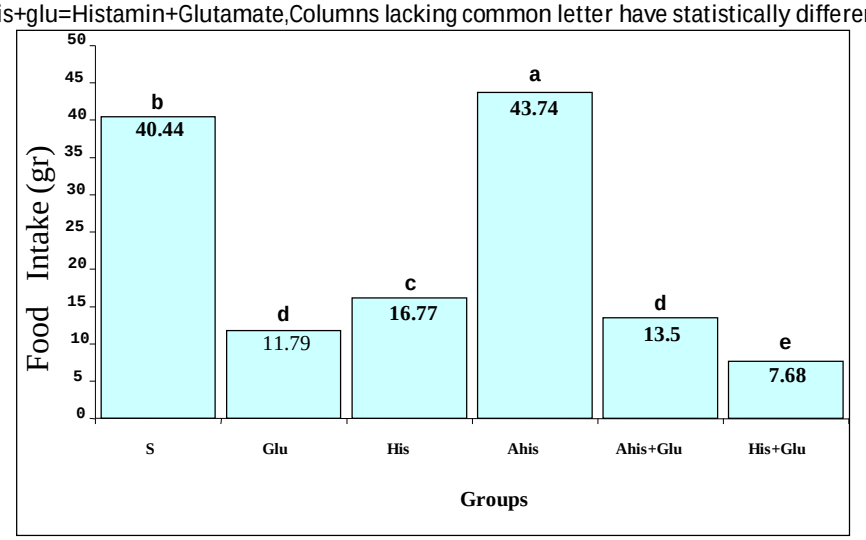

Fig8.Food Intake (gr) in 90min after intraventricular injection S=serum physiology,His=Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05)

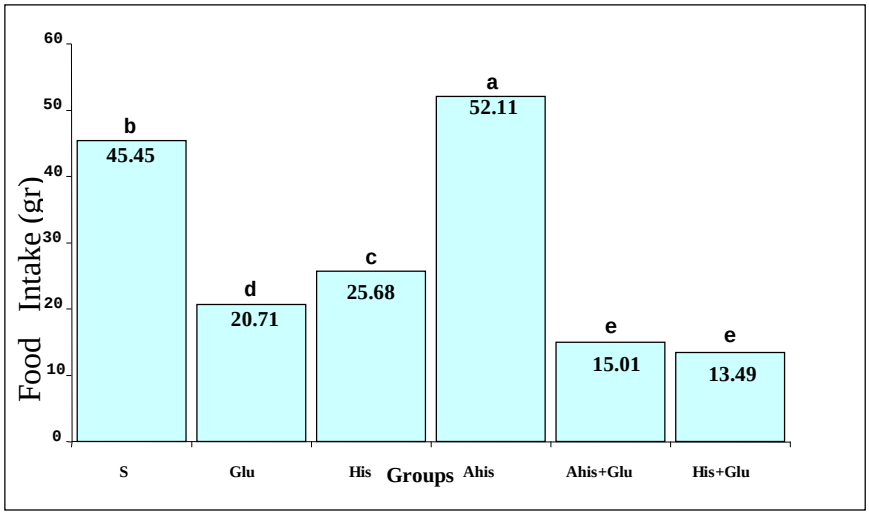

Fig9.Food Intake (gr) in 120min after intraventricular injection S=serum physiology,His=Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05)

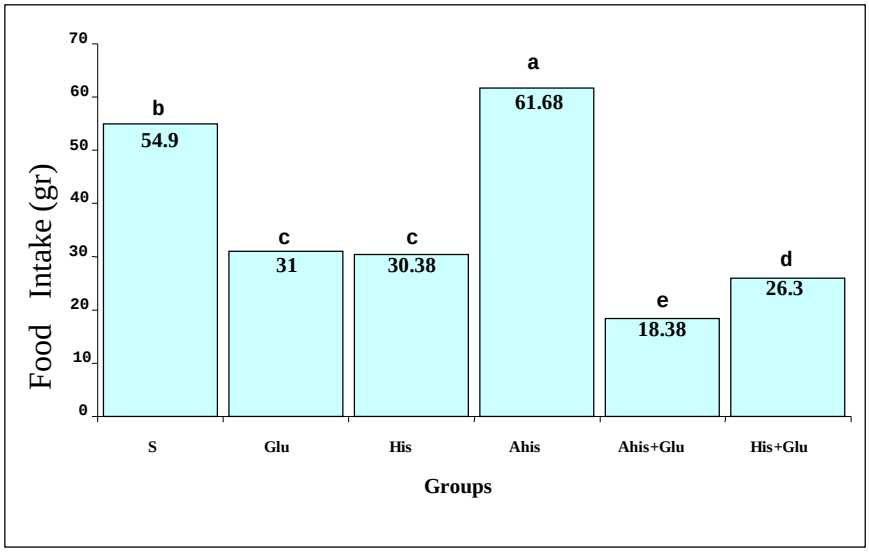

Fig10.Food Intake (gr) in 180min after intraventricular injection S=serum physiology,His=Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05)

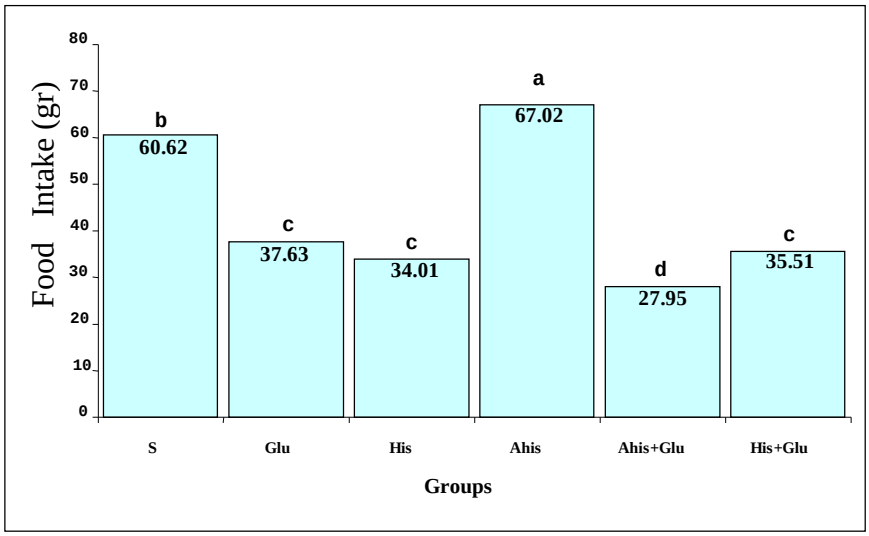

Fig11.Food Intake (gr) in 240min after intraventricular injection S=serum physiology,His=Histamin,Glu=Glutamate,Ahis=Histamine antagonist,Ahis+glu= Histamine antagonist+ Glutamate,his+glu=Histamin+Glutamate,Columns lacking common letter have statistically difference (p<0.05).

DISCUSSION

Many of the classic neurotransmitters have been shown to affect food intake when injected directly into the central nervous system of birds. In present study Glutamate injection considerably decrease food intake compared to control in all times (P<0.05).However the effect of Glutamate in contrast to Histamine in times 60,90 and 120 minutes after injection was significant but in other times these two groups induced the similar nutritional behavior in broilers chickens. The results due to comparison of Glutamate with Histamine+Glutamete indicated that Glutamate group consumed more food in all times rather than Histamine +Glutamate group as in exception of times 15 and 240 in other times these two groups showed significant difference compared together (P<0.05).However the Glutamate group consumed less food compared to Histamine Antagonist group in all times (P<0.05). On the base of a study, the injection of broad-spectrum antagonist of glutamate receptors caused considerable increase of food intake in broilers, justifying the effect of glutamate on appetite decreasing. Similar results were obtained in some other studies [16, 17, 18]. According to a report the negative feed back signals sended by digestive system to central nervous system results(CNS) in satiety and ending to food intake,it is indicated that these signals is tranmitted to CNS via Vagus nerve and intermediation of glutamate receptors(specially NMDA receptors)[19].This report proved mediatory role of glutamate in decrease and stopping of food intake. In the current study histamine reduced food intake in all periods of time compared to control

(P<0.05).This result was in accordance with Denbow and Meade (2001) and some other studies carried out in rat, cat, rabbit and goat [20,21,22] and However, it was not observed a significant difference in minutes 15,30,45 and 240 between groups Histamine and Histamine + glutamate But in the other times differences between these two groups were statistically considerable(P<0.05).Histamine antagonist increased food intake in treatment group compared to control(P<0.05) which is in agreement with Kawakami and et al[15].Concurrent micro-injection of Glutamate and Histamine antagonist induced reduction of food intake in comparison with control(P<0.05).It was cleared that Glutamate + Histamine antagonist consumed more food in contrast with groups Glutamate and Histamine in initial times but in times 180 and 240 minutes after injection the food consumption was considerably reduced in Glutamate + Histamine antagonist compared to group Glutamate and group Histamine. The main purpose of cotemporary injection of Histamine antagonist and Glutamate was clarifying that which of them separately predominated to the other. According to result of present study the effect of Glutamate predominated to Histamine antagonist in all times because the food intake was decreased. However, in initial times Histamine antagonist weekend the effect of Glutamate but in final times. up now there is no report on cotemporary injection of Histamine antagonist and Glutamate .Injection of Histamine+Glutamate solution decreased food intake compared to control considerably(P<0.05) as appetite in times 15,30,45,60,90 and 120 in Histamine+Glutamate group was in at least among other groups. However ,it was respected that Histamine+Glutamate intensify the separately effects of each of them but decreasing effect of Histamine+Glutamate was only a little bit more than reducing effect of separate injections of them. Brown and et al reported that Histamine was able to change and even block the ionic currents mediated by NMDA receptors (Glutamate receptors) and also the higher the concentration of histamine, the more inhibition of ionic currents mediated by NMDA receptors[23] and furthermore, it was well identified that NMDA receptors were effective role in food appetite(17,18). It was indicated by Yamamoto and et al that H3 receptors of Histamine could be capable of controlling and inhibiting of Glutamate releasing and some other neurotransmitters in CNS [24].The studies of Brown[23] and Yamamoto[24] can justify the main reason of lack of respected effect of Histamine+Glutamate on food intake.

CONCLUSION

The results of current study represented that synchronic rise of histamine and glutamate in right ventricle of brain in broilers decreased the food intake, but the rate of this decrease would not be in significant difference with decreasing effect of each of them separately.

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Authors' contributions

All authors participated in the main research and Javad cheraghi performed the literature review, drafted the manuscript. Ehsan Hosseini performed manuscript writing. All authors have read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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