Original Article

Sericin-Induced Hypophagia Mediates Via M_1 Muscarinic, NMDA Glutamate and Glycine Receptors in Neonatal Chicken

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ABSTRACT

The objective of this study was to ascertain the interaction between muscarinic, NMDA glutamate, and glycine receptors on sericin-induced hypophagia in neonatal chickens. This study comprised six experiments, with four groups in each and 11 repeats per group. In Experiment 1, the chicken received an ICV injection of saline, sericin (0.5 nmol), or Telenzepine (an M1 muscarinic receptor antagonist, 125 nmol). Group 4 received a co-injection of sericin and Telenzepine. In experiments 2-6, the chicken received ICV injections of AF-DX116 (an M2 muscarinic receptor antagonist, 125 nmol), 4-DAMP (an M3 muscarinic receptor antagonist, 125 nmol), PD102807 (an M4 muscarinic receptor antagonist, 125 nmol), MK-801 (an NMDA glutamate receptor antagonist, 15 nmol), and strychnine (a glycine receptor antagonist, 100 nmol) instead of Telenzepine. Subsequently, the cumulative food intake was quantified at 30, 60, and 120 minutes post-injection. The results demonstrated that the ICV injection of sericin (0.5 nmol) led to a notable reduction in cumulative food intake when compared to the control group ($P<0.05$). The co-injection of telenzepine and sericin resulted in a notable reduction in the hypophagia induced by sericin, as evidenced by a statistically significant difference ($P<0.05$). The co-injection of MK-801 and sericin resulted in a reduction of the hypophagic effects of sericin when compared to the control group ($P<0.05$). The co-injection of strychnine and sericin resulted in a notable reduction in the hypophagic effects of sericin, as evidenced by a statistically significant difference when compared to the control group ($P<0.05$). These findings suggest that sericin-induced hypophagia is mediated via M1 muscarinic, NMDA glutamate, and glycine receptors in neonatal chickens.

Keywords: Sericin, Muscarinic, Glutamate, Glycine, Food intake, Chicken.

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1. Introduction

Modern broiler chickens, which have been selectively bred for rapid growth and high meat production, exhibit hyperphagia. Consequently, the excessive intake of food may result in the accumulation of visceral fat, which is regarded as an animal byproduct or waste. Furthermore, an excess of adipose tissue may precipitate the development of metabolic disorders, which could present significant challenges for the poultry sector. In light of these considerations, research efforts in recent decades have been directed towards elucidating the regulatory mechanisms underlying appetite in chickens (1). The regulation of food intake in animals such as domestic birds is a complex process. Immediately following hatching, baby chicks are capable of locating their own food and regulating their intake, as they are part of the precocial category of birds that includes domestic chickens. Consequently, at the time of hatching, domestic chickens exhibit a relatively sophisticated regulatory system for food intake (2). The regulation of food intake is governed by a combination of physiological signals originating from both central and peripheral sources. The hypothalamus, brainstem, and endocannabinoids act as the primary regulators of food intake, while satiety and adiposity signals exert control from the periphery (1). The silkworm (Bombyx mori) produces two principal proteins in its silk: sericin and fibroin. L-serine, a primary amino acid in sericin, constitutes approximately 40% of all amino acid codons in the mRNA sequence, thereby conferring the protein with its adhesive properties. Recent research indicates that this protein has a range of health benefits, including antioxidant properties, enhancement of lipid and carbohydrate metabolism, and dietary fiber-like qualities due to its low digestibility (3). The biological properties of sericin render it an optimal candidate for utilization as an additive in cosmetics, cell preservation, and a multitude of commercial applications. Sericin administration has been demonstrated to elevate the levels of L-serine and L-tyrosine in both the serum and the brain. Furthermore, the introduction of sericin resulted in a notable increase in noradrenergic turnover, as evidenced by a significant elevation in 3-methoxy-4-hydroxyphenylethyleneglycol levels (4). The cholinergic systems located in both the central and peripheral regions play a pivotal role in numerous physiological processes, including cognitive function, behavioral patterns, sensory perception, food intake, and energy homeostasis. Six distinct types of mAChRs have been identified in neurons and other cellular elements. The M1, M4, and M5 receptors are predominantly expressed in the central nervous system, whereas the M2 and M3 receptors are present in both central and peripheral tissues (5). Research has indicated that the M1 and M3 subtypes play a role in regulating energy metabolism and maintaining stable blood glucose levels in mammals (6). Furthermore, the administration of a muscarinic M3 receptor antagonist via intracerebroventricular injection in mice was observed to result in a reduction in food intake. Furthermore, the anorexigenic impact of the muscarinic system is purported to be regulated by M1 and M3 receptors in neonatal broiler chickens (7). Glutamate is the primary excitatory neurotransmitter in the brain, and the administration of N-methyl-d-aspartate (NMDA) antagonists has been observed to increase food intake in satiated rats. Injection of N-methyl-d-aspartate (NMDA) receptor antagonists into ventral striatal and ventral pallidal areas has been observed to increase food intake in pigeons and broilers (8). Glycine is an inhibitory neurotransmitter that is detectable in the central nervous system. Two distinct types of ligand-gated ion channels have been identified: glycine receptors, which permit the passage of chloride ions, and NMDA receptors, which allow for the selective permeation of cations. Both types of channels can be activated by glycine (9). The inhibitory effect of glycine is attributable to its binding to chloride channels, which results in the hyperpolarization of neurons. The hypophagic effect observed in chickens is attributed to the release of glycine from nerve terminals and its subsequent binding to glycine receptors in the postsynaptic space (10). Although certain aspects of food intake regulation in chickens bear resemblance to those observed in mammals, there are notable differences in the central regulation of food intake between these two species. A review of the literature reveals a paucity of information regarding the role of sericin in the central regulation of food intake. Therefore, the objective of this study was to ascertain the interaction between muscarinic, NMDA glutamate, and glycine receptors on sericin-induced hypophagia in neonatal chickens.

Food intake

2. Materials and Methods

2.1. Birds

The present study employs 264-day-old meat-type chickens (Ross-308 breed) sourced from a local hatchery (Mahan Co., Iran). The juvenile birds were housed collectively for a two-day interval under a photoperiod of 23 hours of illumination and 1 hour of darkness at a temperature of 31±2°C, with humidity levels maintained at 50%±2%. Subsequently, they were housed individually for a period of five days. The birds were permitted to drink freely from a source of fresh water and consume a commercial diet with a crude protein content of 21% and a metabolizable energy density of 2850 kcal/kg.

2.2. ICV Injection

The injection of ICV was performed when the subject was five days old. To inject the cerebral ventricle of chickens, a conscious chick's head was secured with a 45-degree angled acrylic device, ensuring that the skull surface was level with the workbench surface. A stencil was punctured and promptly positioned over the skull in the right ventricular region (11). The remedies were administered via puncture, created with a Hamilton syringe. The needle tip was only 4 mm deep within the skin and skull. The process is not perceived as stressful by the chickens. Saito et al. (12)

administered 10 microliters of injection in each group. After the experiments, decapitation was performed to evaluate the accuracy of the injections. Evans Blue in the brain tissue served to confirm the accurate positioning of the injection in the ventricle, as previously stated by Furuse et al. (13).

2.3. Food Intake Measurement

This study comprised six experiments, with four groups in each experiment and 11 repeats for each group. The chicks were deprived of food for a period of three hours (FD3) prior to the commencement of the experiment. Following the injection, the chicks were returned to their cage and were permitted free access to water and food. In Experiment 1, the chicken received an ICV injection of saline, sericin (0.5 nmol), and Telenzepine (M1 muscarinic receptor antagonist, 125 nmol). In Group 4, a co-injection of sericin and Telenzepine was applied. In Experiment 2, the injection of saline, sericin (0.5 nmol), AF-DX116 (M2 muscarinic receptor antagonist, 125 nmol), and the co-injection of sericin and AF-DX116 were conducted. In Experiment 3, the chicken received an ICV injection of saline, sericin (0.5 nmol), 4-DAMP (M3 muscarinic receptor antagonist, 125 nmol), and a co-injection of sericin and 4-DAMP. In Experiment 4, the ICV injection was administered as a saline solution, sericin (0.5 nmol), PD102807 (M4 muscarinic receptor antagonist, 125 nmol), and a co-injection of the sericin and PD102807. In Experiment 5, the injection of saline, sericin (0.5 nmol), MK-801 (an NMDA glutamate receptor antagonist, 15 nmol), and the co-injection of sericin and MK-801 were conducted. In Experiment 6, an ICV injection of strychnine (a glycine receptor antagonist, 100 nmol), sericin (0.5 nmol), and a combination of sericin and strychnine was conducted. Subsequently, the cumulative feed amount was quantified at 30, 60, and 120 minutes post-injection. Furthermore, food intake was expressed as a percentage of body weight in order to minimize the impact of weight differences between chickens on food intake (11, 14).

2.4. Statistical Analysis

All data were initially processed using the Excel 2016 software. The statistical analyses were conducted using the statistical software SPSS 25.0, and the results are presented as mean±standard error of the mean (SEM). The statistical analyses were conducted using a one-way analysis of variance (ANOVA) followed by Tukey's test. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

As illustrated in Figure 1, the administration of sericin (0.5 nmol) via ICV resulted in a notable reduction in cumulative food intake when compared to the control group ($P<0.05$). Telenzepine (125 nmol) did not affect cumulative food intake compared to the control group ($P<0.05$). The co-injection of Telenzepine and sericin resulted in a significant reduction in the hypophagia induced by sericin ($P<0.05$). As illustrated in Figure 2, sericin (0.5 nmol) exhibited a notable reduction in cumulative food intake when compared to the control chicken group ($P<0.05$). The administration of AF-DX116 (125 nmol) did not result in a statistically significant difference in cumulative food intake when compared to the control group ($P<0.05$). The co-injection of AF-DX116 and sericin did not result in any discernible impact on the hypophagic effect of sericin, as evidenced by a p-value exceeding 0.05. As illustrated in Figure 3, the administration of sericin (0.5 nmol) resulted in a notable reduction in cumulative food intake when compared to the control group of chickens ($P<0.05$). The administration of 4-DAMP (125 nmol) did not result in a statistically significant difference in cumulative food intake when compared to the control group ($P<0.05$). The co-injection of 4-DAMP and sericin did not result in any observable effect on the sericin-induced hypophagia ($P>0.05$). As illustrated in Figure 4, sericin (0.5 nmol) exhibited a notable reduction in cumulative food intake when compared to the control chicken group ($P<0.05$). PD102807 (125 nmol) had no effect on cumulative food intake compared to the control group ($P<0.05$). The co-injection of PD102807 and sericin did not result in any observable effect on the sericin-induced hypophagia ($P>0.05$). As illustrated in Figure 5, food intake exhibited a notable decline following ICV injection of sericin (0.5 nmol) in comparison to the control group ($P<0.05$). The ICV injection of MK-801 (15 nmol) did not result in a statistically significant difference in cumulative food intake compared to the control group ($P<0.05$). The co-injection of MK-801 and sericin resulted in a reduction of the hypophagic effects of sericin, as evidenced by a statistically significant difference ($P<0.05$) when compared to the control group. Additionally, a reduction in food intake was observed following the ICV injection of sericin (0.5 nmol) when compared to the control group ($P<0.05$). The ICV injection of strychnine (100 nmol) did not result in any significant alteration in cumulative food intake when compared to the control group ($P<0.05$). The co-injection of strychnine and sericin resulted in a reduction of the hypophagic effects of sericin, as evidenced by a statistically significant difference when compared to the control group ($P<0.05$) (Figure 6).

4. Discussion

The principal outcome of the present study was that ICV injection of sericin resulted in a reduction in cumulative food intake. The co-injection of telenzepine and sericin resulted in a reduction in the hypophagic effects of sericin. The co-injection of MK-801 and sericin resulted in a reduction of the hypophagic effects of sericin. The co-injection of strychnine and sericin resulted in a reduction of the hypophagic effects of sericin. The available evidence indicates that sericin plays a physiological role in food intake and appetite regulation. Additionally, sericin has been demonstrated to diminish serum cholesterol levels in rats and augment cognitive function in patients with Alzheimer's disease (15).

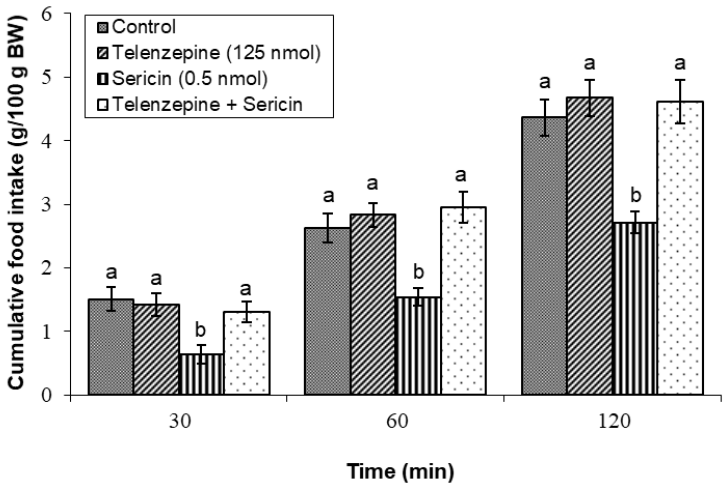

Figure 1. Effect of ICV injection of Telenzepine (125 nmol), Sericin (0.5 nmol) and their combination on cumulative food intake in neonatal chickens (n=44). Telenzepine: M_1 muscarinic receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.05$).

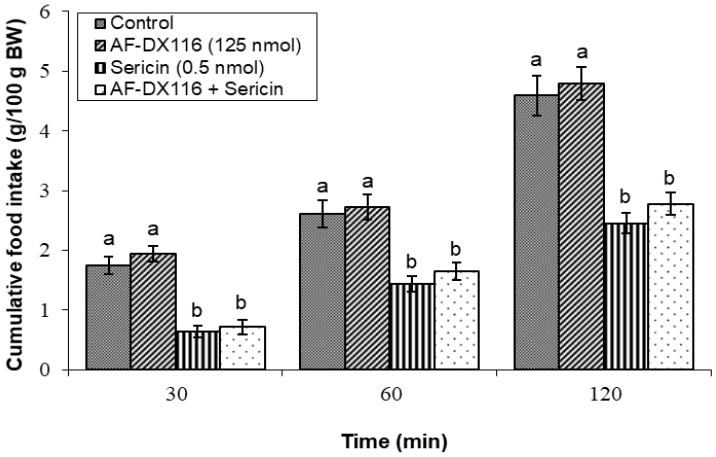

Figure 2. Effect of ICV injection of AF-DX116 (125 nmol), Sericin (0.5 nmol) and their combination on cumulative food intake in neonatal chickens (n=44). AF-DX116: M_2 muscarinic receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.05$).

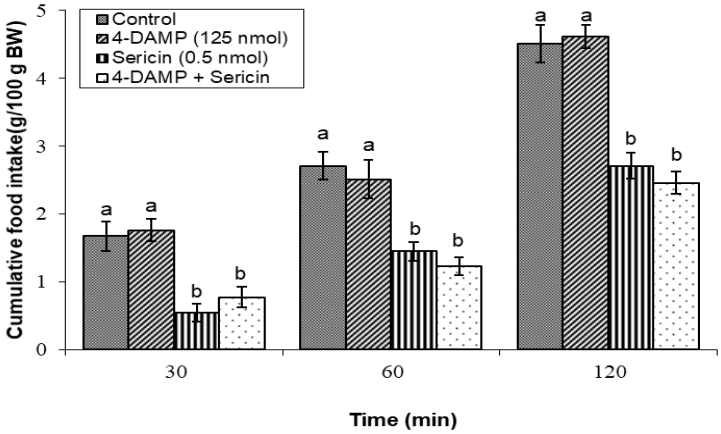

Figure 3. Effect of ICV injection of 4-DAMP (125 nmol), Sericin (0.5 nmol) and their combination on cumulative food intake in neonatal chickens (n=44). 4-DAMP: M_3 muscarinic receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.05$).

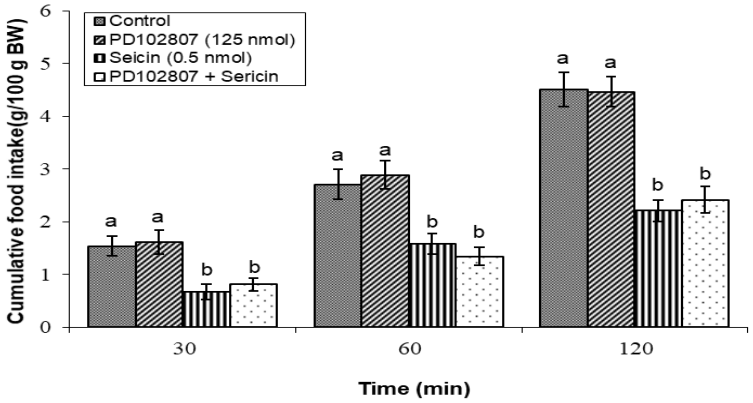

Figure 4. Effect of ICV injection of PD102807 (125 nmol), Sericin (0.5 nmol) and their combination on cumulative food intake in neonatal chickens (n=44). PD102807: M_4 muscarinic receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.05$).

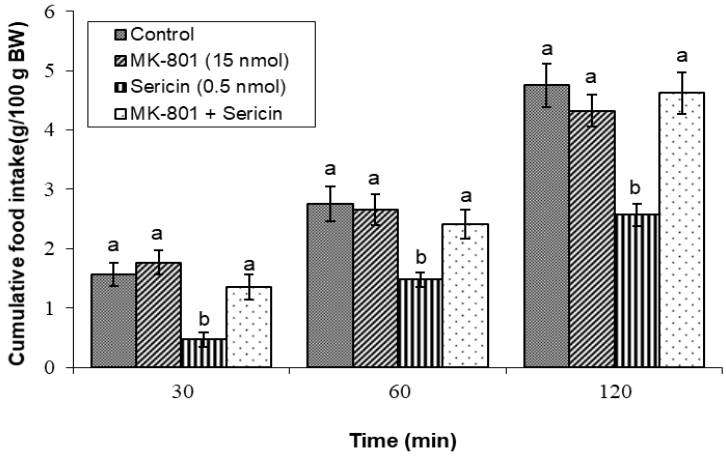

Figure 5. Effect of ICV injection of MK-801 (15 nmol), Sericin (0.5 nmol) and their combination on cumulative food intake in neonatal chickens (n=44). MK-801: NMDA glutamate receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.05$).

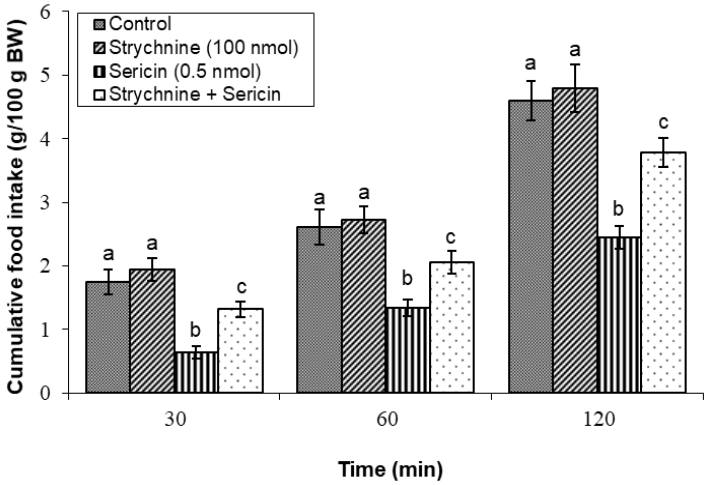

Figure 6. Effect of ICV injection of Strychnine (100 nmol), Sericin (0.5 nmol) and their combination on cumulative food intake in neonatal chickens (n=44). Strychnine: glycine receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.05$).

Sericin has been demonstrated to exert a pronounced anti-hyperglycemic effect. A recent report indicates that sericin supplementation can effectively reduce blood sugar levels in a streptozotocin-induced type 2 diabetic mouse model (16). Sericin water has been demonstrated to enhance the insulin-PI3K/AKT signaling pathway in the livers of rats with type 2 diabetes (17). In a rat model, it was observed that sericin decreased neuronal cell death in the hippocampus by activating the AKT signal transduction pathway, thereby providing neuroprotection in diabetic rats. The oral administration of sericin was observed to enhance the antioxidant capacity of diabetic rats, which was subsequently accompanied by a notable reduction in the levels of inflammatory substances within their bodies. This reduction resulted in alterations to the regulation of genes and proteins involved in the production of insulin, glucose synthesis, and breakdown, glycogen formation and storage, as well as fat synthesis and metabolism (18). The inhibitory impact of sericin on free fatty acids is linked to enhanced glucose absorption in peripheral tissues, which in turn results in improved glucose tolerance. It has been demonstrated that the addition of 2% sericin to the diet of rats results in a significant reduction in oxidative stress. It has recently been demonstrated that sericin enhances antioxidant activity in rats by inhibiting tyrosinase. Sericin has been demonstrated to exert a laxative effect by promoting the excretion of fecal nitrogen, thereby increasing bowel movements in rats. Furthermore, it has been demonstrated to enhance the absorption of zinc, magnesium, and iron in the intestines, thereby increasing the bioavailability of these trace elements (19). PI3K activates a serine/threonine protein kinase, Akt, which is involved in the translocation of glucose transporter 4 (GLUT4) to the cell membrane. Further research is currently being conducted to ascertain whether the addition of sericin can facilitate enhanced glucose transport in tissue by stimulating PI3K Akt-mediated GLUT4 translocation (20). The M1 and M3 receptors demonstrate high levels of expression in the hypothalamic (VMH) and arcuate nuclei (ARC) regions of the hypothalamus. The administration of olanzapine via intracerebroventricular (ICV) injection in rats, which acts as a muscarinic M3 receptor antagonist, resulted in a notable increase in food consumption. Studies on animals have demonstrated the existence of potential connections between the muscarinic system and a variety of hormones and neurotransmitters. The cholinergic nerve supply from the vagus nerve, which connects the brain to the digestive system in rats, suggests the potential involvement of M3 receptors in the regulation of gastrointestinal hormones (5). The density of brain M3 receptors was found to be associated with alterations in ghrelin and CCK levels in rat plasma. Furthermore, evidence suggests that M1 and M3 receptors in the brain function to reduce appetite by inhibiting the neuropeptide Y (NPY) in the ARC (21). Additionally, NMDA receptors are expressed in NPY/agouti-related protein (AgRP) and proopiomelanocortin (POMC) neurons of the hypothalamus. NMDA receptors have been demonstrated to play a role in the regulation of appetite and feelings of satiety. Neurons employ glutamate as a co-transmitter, which functions through AMPA/kainate-mediated excitatory postsynaptic potentials. Therefore, it seems that a specific aspect of the influence exerted by these neurotransmitters may manifest comparably with regard to feeding behavior in broiler chickens (8). Silk sericin intake has been demonstrated to result in increased levels of L-serine and L-tyrosine in the mouse brain, accompanied by a simultaneous facilitation of brain noradrenergic turnover (3). L-serine is classified as a non-essential amino acid from a nutritional standpoint. In the brain, it is converted to D-serine through an enzymatic process involving the enzyme serine racemase. D-serine functions as the co-agonist of N-methyl-D-aspartate (NMDA) receptors, which are extensively expressed in the central nervous system and are crucial mediators of synaptic transmission in various physiological and pathological processes (22). It is therefore essential to maintain the level of L-serine in the brain, as this is critical for the brain-related processes that are mediated by D-serine and NMDA receptors. L-Tyr is a requisite precursor of the catecholamine neurotransmitters dopamine and noradrenaline, and its administration has been demonstrated to stimulate catecholamine synthesis in the brain (23). The available evidence suggests that there is an interaction between central muscarinic, N-methyl-D-aspartate (NMDA), and glycine receptors. Upon activation by glutamate (in the presence of glycine), NMDA receptors typically contribute to membrane depolarization and Ca^{2+}-dependent signaling cascades by increasing the conductance of Na^{+} and Ca^{2+}. NMDA receptors are typically located on neuronal postsynaptic membranes, but they have also been identified on presynaptic terminals, where they modulate the release of GABA and glutamate. NMDA receptors situated on synaptic terminals (i.e., pre-NMDA receptors) are activated in a constitutive manner by ambient glutamate (24). NMDA receptors transduce signaling via both glycine and glutamate binding, signaling via glycine binding, and signaling by glutamate binding (25). To date, no research has been conducted on the ICV injection of sericin and its interaction with muscarinic, NMDA glutamate, and glycine receptors on food intake in chickens. A review of the literature suggests the existence of interconnections between central muscarinic NMDA glycine receptors, which may play a role in regulating food intake. It is our contention that this primary information is beneficial for the study of central food intake regulation in birds. Due to the limitations of the study, a comparison with previous reports could not be made. The findings indicated that sericin-induced hypophagia is mediated via M1 muscarinic, NMDA glutamate, and glycine receptors in neonatal chickens. Further research is required to determine additional information.

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Authors' Contribution
Collect data, the draft of the paper: N.M.
Thesis supervisor, revision of the paper, study design: M.Z.
Thesis supervisor: B.V.
Thesis advisor, revision of the paper, study design: S.H.

Ethics
We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest
The authors declare that they have no conflict of interest.

Data Availability
The data that support the findings of this study are available on request from the corresponding author.

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