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Alteration of stress response and expression of carbohydrate metabolic genes by exogenous insulin during slaughter of domestic birds

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ABSTRACT

Aim: This study investigates the role of exogenous insulin (INS) in modulating stress responses in domestic birds during slaughter. The research explores INS's potential in reducing stress markers and its effects on gene expression related to glucose transport and INS regulation.

Methods: A total of 45 birds, including broiler chickens, Sonali chickens, and quails, were divided into three treatment groups. They received either 4 IU or 8 IU of INS, or phosphate-buffered saline as a control. Thirty minutes after administration, blood, liver, and pancreas samples were collected for analysis. Stress markers such as the heterophil-to-lymphocyte (H:L) ratio and serum cortisol levels were measured, along with the expression of key genes, including GLUT12, insulin receptor (IR), and INS.

Results: INS administration significantly reduced the H:L ratio across all bird species, indicating a stress-reducing effect. While cortisol levels decreased in Sonali chickens, broilers exhibited an unexpected rise in cortisol at lower INS doses, suggesting species-specific variations. Additionally, INS upregulated GLUT12 gene expression in both the liver and pancreas, enhancing glucose transport. Increased IR expression was observed in the liver, and INS administration stimulated its own transcript (INS) in the pancreas, suggesting a self-regulatory mechanism.

Conclusion: These findings highlight INS's potential in mitigating slaughter-induced stress in poultry. Its effects on cortisol regulation and GLUT12 expression suggest a broader physiological role beyond glucose metabolism. Incorporating INS-based interventions could offer new strategies for improving animal welfare in the poultry industry.

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Introduction

The poultry industry is a critical component of the global food supply, providing a substantial source of protein [1]. Therefore, millions of chickens are slaughtered worldwide every day. However, the process of slaughtering birds, such as chickens and turkeys, can be a stressful experience for the animals. Stress during slaughter can not only affect animal welfare but also have implications for the quality and safety of the meat produced [2]. One critical aspect of this stress response is the alteration of carbohydrate metabolism in birds, which is known to occur under stressful conditions [3].

Carbohydrate metabolism is tightly regulated in birds and is crucial for maintaining energy levels during periods of stress. One key hormone involved in regulating carbohydrate metabolism is insulin (INS), which plays a central role in controlling

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blood glucose levels [4]. INS is primarily produced in the pancreas and is responsible for facilitating the uptake of glucose into cells, where it can be used for energy production or stored for later use. In situations of stress, the normal regulation of INS and glucose metabolism can be disrupted, leading to changes in the energy balance of the bird [5].

While exogenous INS administration has been studied extensively in humans for diabetes management, its application in stress management remains unexplored. Previous research in the field of endocrinology has provided valuable insights into the role of INS in regulating carbohydrate metabolic genes in different species [6].

Despite extensive research on stress responses during slaughter and their impact on meat quality and animal welfare, the role of INS in modulating these stress responses remains largely unexplored. Existing studies primarily focus on INS's role in carbohydrate metabolism and its regulatory functions in glucose homeostasis [7], but its application in alleviating stress, especially in poultry, has received little attention. Previous research has highlighted the detrimental effects of stress on both animal welfare and the economic sustainability of the poultry industry, with alterations in stress markers such as the heterophil-to-lymphocyte (H:L) ratio and cortisol levels being widely recognized [7]. However, there is a clear research gap regarding the potential of exogenous INS administration to influence these stress markers and modulate gene expression associated with glucose transport [8].

This study addresses this gap by investigating how INS can reduce stress during the slaughter process and its novel effects on carbohydrate metabolic gene expression, offering insights into new strategies for improving poultry welfare and meat quality. Furthermore, while stress management strategies in poultry have focused on environmental and handling factors [9], INS's capacity as a biochemical modulator presents a unique, underexplored avenue that could revolutionize current practices in animal welfare and production efficiency.

The stress response in birds during the pre-slaughter period is a complex and multifaceted phenomenon that involves the activation of various physiological and biochemical pathways. These pathways can lead to changes in blood glucose levels and the expression of carbohydrate metabolic genes in various tissues [7]. By introducing exogenous INS, we aim to examine how it might influence the stress response in birds during slaughter and potentially modulate carbohydrate metabolic gene expression. It could provide valuable insights into the potential use of exogenous INS to mitigate the stress response in birds during slaughter, which could have implications for both animal welfare and the poultry industry's economic sustainability.

Materials and Methods

Ethical approval

The ethical approval (CVASU/Dir (R&E) EC/2023/500/9) was taken from "Institutional Ethical Committee" of Chattogram Veterinary and Animal Sciences University (CVASU), Bangladesh. The animals used in this study were treated according to the standard guidelines.

Study area and animals

A total of 45 live birds were procured from a local live bird market in Chattogram, Bangladesh, for this study. The birds included 15 commercial broiler chickens (Cobb 500) aged 35 ± 5 days, 15 Sonali chickens (a crossbreed of Fayoumi females and Rhode Island Red males) aged 65 ± 5 days, and 15 Japanese quails aged 30 ± 5 days. All birds were housed at a room temperature of 25°C. They were reared in groups of five per cage, with each cage providing a total floor space of 4 square feet.

INS treatment, slaughtering, and sample collection

The birds of each group were divided into three subgroups according to the treatment they received. Therefore, there were three groups for each category of birds (broiler chicken/Sonali chicken/Quail). The birds were kept fasting for 8 hours and after that, each five birds of three different groups subcutaneously received INS (Ansulin 30/70, Square Pharmaceuticals Ltd. Bangladesh) at a dose of 4 and 8 IU, respectively. Another five birds received phosphate buffer saline as control. Thirty minutes after injection, the birds were slaughtered by severing the neck vessels at the level of atlanto-occipital joint without stunning, and blood samples were collected for analysis. Collected blood samples were kept in a vacutainer with ethylenediaminetetraacetic acid (EDTA) and without anticoagulant. The blood without anticoagulant was used for serum separation by spinning the coagulated blood at 3,000 rpm for 30 minutes and stored the collected serum at −80°C until analysis. After that, the respective liver and pancreas were collected and immediately snap frozen in liquid nitrogen and stored in −80°C until gene expression analysis.

White blood cell count

Direct blood smears were made from EDTA-containing blood and these were stained using Wright's stain. The stained smear was observed under a light microscope to count the number of H:L. The number of heterophils was divided by a number of lymphocytes to express values as H: L ratio as an indicator of stress.

Estimation of glucose and cortisol

The collected and stored serum was used to measure the concentration of glucose and cortisol levels. The level of glucose was analyzed by a commercial kit (Glucose-GOD PAP, #87409, Biolabo, France), according to manufacturer's protocol using a biochemical analyzer (Humalyzer-3000, Germany). Serum cortisol levels in the experimental birds were measured by an immunofluorescence analyzer (Anbio Biotech, China) as described in the manufacturer's protocol. Briefly, 100 µl of serum was loaded into the respective well of the cortisol kit and incubated for 15 minutes. After 15 minutes, the cortisol kit was checked by the analyzer and the concentration of cortisol was measured.

Gene expression analysis

Total RNA was extracted from the liver and pancreas using easy-BLUE™ Total RNA extraction kit (#17061, Intron Biotechnology, Seongnam-si, South Korea) according to the manufacturer's protocol. The RNA concentration and quality were measured using a NanoDrop spectrophotometer (Thermoscientific, USA). Five hundred ng of total RNA was reverse transcribed using ABScript II cDNA first-strand synthesis kit (#RK20400, ABclonal, USA) according to the manufacturer's protocol. Reverse-transcribed samples were subjected to quantitative real-time PCR (qPCR). The mRNA expression of the *GLUT12,* insulin receptors (*IR)* in the liver, and INS and GLUT12 in the pancreas was investigated. The β-actin (ACTB) was used as the reference gene to normalize the expression of the target gene. The primer sequences used in qPCR are listed in Table 1. The qPCR reaction mixture was arranged using GoTaq qPCR Master Mix (#A6001, Promega, Japan) according to the manufacturer's protocol in a 25 µl reaction volume. After that, samples were run on a 7,500 fast real time PCR system (Applied Biosystems, USA). The qPCR conditions were set as follows: denaturation at 95°C for 10 seconds, followed by 40 cycles of denaturation at 95°C for 5 seconds, annealing at 60°C for 30 seconds, and elongation at 72°C for 15 seconds. The relative quantification of the target genes and reference gene was evaluated according to standard curves. The calculation of relative gene expression was done using the calibration curve method, where C_T is the threshold cycle.

Data analysis

The data obtained in the study was stored in MS Excel 2019. Data were then sorted, cleaned, and exported to STATA-11. Then the level of glucose, hemoglobin, H:L ratio, and cortisol was expressed as mean, standard error. The comparative analysis among control and two dosages INS groups was performed by using a one-way analysis of variance. To understand the differences between groups, data were compared with Tukey's Honest Significance Difference test. A *p* value less than 0.05 was considered as significant difference in every case.

Results and Discussion

INS administration mitigates slaughter-induced stress in domestic birds

To investigate the impact of exogenous INS on stress responses during slaughter, recombinant INS was administered to broiler chickens, Sonali chickens,

Table 1. List of primers used for qPCR.

Gene	NCBI accession no	Direction	Sequence (5' - 3')	Amplicon (bp)
GLUT12	XM_419733.7	Forward	TGGGGTCTCACACAGAGAGT	120
		Reverse	GGACGAGCCAAGACATTGGT	
IR	XM_001233398.7	Forward	CCAGCTCTCCCTTCACGATG	131
		Reverse	CAGTGATGTGTACGTTCCCGA	
INS	NM_205222.3	Forward	CAAGGGACTGCTCACTAGGGG	72
		Reverse	GGAGAGCGTGGCTTCTTCTA	
ACTB	NM_205518.2	Forward	ACCACAGGACTCCATACCCAA	70
		Reverse	TGGCAATGAGAGGTTCAGGT	

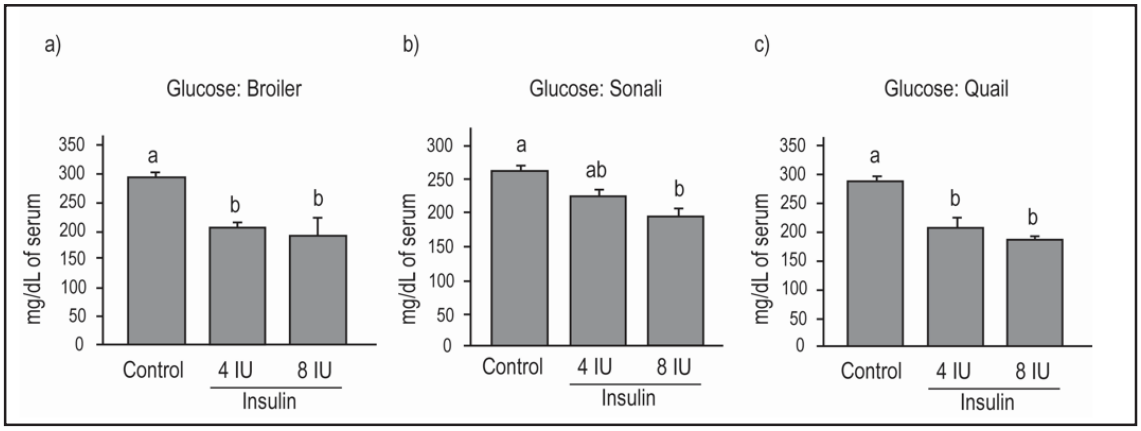

Figure 1. The serum glucose levels birds after INS administration. a) Broiler chicken b) Sonali chicken and c) Quail. Birds were injected subcutaneously with 0, 4, and 8 IU INS and serum glucose levels were measured after 30 minutes of injection. The data represent the mean ± SEM (*n* = 5), and bars with different superscripts differ significantly.

and quails at two distinct doses (4 and 8 IU), 30 minutes prior to slaughter. Following the slaughter process, blood samples were collected from the severed neck vessels to measure H:L ratios and serum cortisol levels. INS administration significantly reduced blood glucose concentrations across all bird types, confirming its physiological efficacy (Fig. 1A–C). Notably, the H:L ratios—which serve as an established indicator of stress—were significantly lower in INS-treated groups compared to controls, irrespective of bird type (Fig. 2A–C). Furthermore, serum cortisol levels were significantly reduced in INS-treated Sonali chickens compared to their respective controls (Fig. 3B), underscoring the potential role of INS in mitigating slaughter-induced stress. However, in broiler chickens, INS administration did not exhibit a cortisol-lowering effect; on the contrary, cortisol levels were elevated following treatment (Fig. 3A).

Although INS is primarily recognized for its role in maintaining glucose homeostasis and regulating carbohydrate and lipid metabolism, emerging evidence suggests that it may also influence stress responses. Studies in rodent models have demonstrated that INS administration can attenuate stress-induced activation of the hypothalamic–pituitary–adrenal (HPA) axis, the central regulator of cortisol secretion. By suppressing the HPA axis, INS may help alleviate the adverse effects of stressors [10].

We have observed a good interplay between INS and cortisol in Sonali chickens a popular breed known for their appreciable levels of productivity and high environmental adaptability, are susceptible to various stressors that can negatively impact their well-being and productivity. Stress in poultry can lead to the release of cortisol, a hormone associated with the body's stress response. Managing stress and cortisol levels is crucial to maintaining the health and productivity of Sonali chickens. In recent studies, there has been emerging evidence suggesting that INS, a hormone primarily known for its role in glucose regulation, may have the potential to decrease stress and cortisol levels in Sonali chickens [11]. In broiler chicken, we have observed that upon administration of INS in low dose (4 IU) the cortisol synthesis increased which is out of our expectation. However, these increases were suppressed to normal levels in higher doses of INS (8 IU). One of the explanations of this phenomena could be the fact of stress susceptibility of broiler chicken. Some rapid growing animals such as broiler chicken and pigs are stress susceptible and the molecular mechanism of their stress susceptibility is incompletely understood [10,11]. The contradictory findings on cortisol in our study could be due to the differences in stress regulation in stress susceptible broiler.

Cortisol, often referred to as the "stress hormone," is released in response to various stressors. Chronically elevated cortisol levels can have detrimental effects on the health and performance of Sonali chickens. INS has been found to interact with cortisol through multiple pathways, suggesting a potential regulatory role. INS administration has been shown to decrease cortisol production by influencing the activity of key enzymes involved in cortisol synthesis and metabolism. Additionally, INS may indirectly affect cortisol levels by promoting glucose uptake in tissues, thus preventing excessive

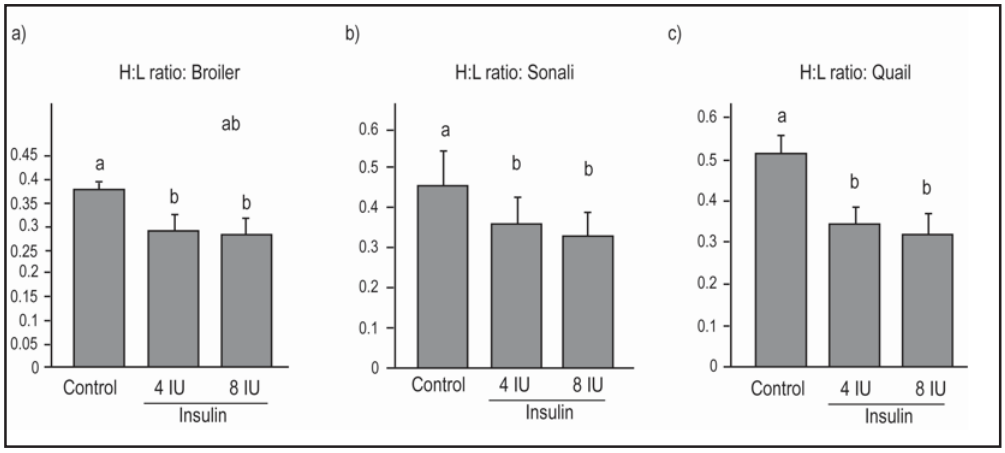

Figure 2. H:L ratio in birds after INS administration. a) Broiler chicken b) Sonali chicken and c) Quail bird. Birds were injected subcutaneously with 0, 4, and 8 IU INS and H:L ratios were measured after 30 minutes of injection. The data represent the mean ± SEM (*n* = 5), and bars with different superscripts differ significantly.

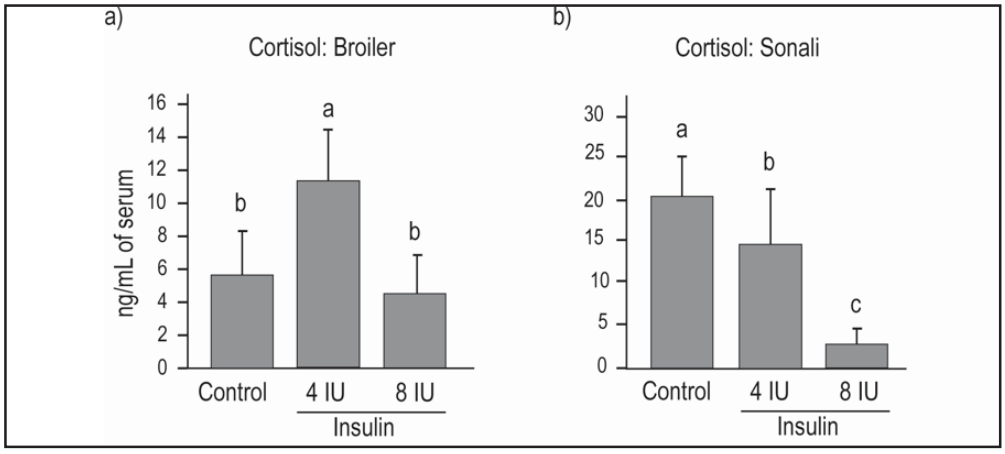

Figure 3. Serum cortisol levels in birds after INS administration. a) Broiler chicken and b) Sonali chicken. Birds were injected subcutaneously with 0, 4, and 8 IU INS and serum cortisol levels were measured after 30 minutes of injection. The data represent the mean ± SEM (*n* = 5), and bars with different superscripts differ significantly.

glucose availability, which can stimulate cortisol secretion [12].

Besides that, the H:L ratio decreased significantly ($p < 0.05$) in all the studied bird species which is quite interesting. The H:L is a commonly used indicator of stress and immune function in poultry. INS, primarily recognized for its role in glucose regulation, has been found to exert modulatory effects on the immune system. It plays a vital role in maintaining immune homeostasis and promoting immune cell function. IRs are present on immune cells, including H:L, indicating that INS may directly influence their activity. INS administration has been shown to enhance the proliferation and activity of lymphocytes while reducing the activation of heterophils, thereby potentially balancing the H:L [13].

INS has been found to decrease the neutrophil: lymphocyte ratio in various animal models, suggesting a potentially similar effect in Sonali chickens. Stressors can disrupt the delicate balance of the immune system, leading to alterations in the H:L. Chronic stress can elevate the H:L, indicating increased stress and compromised immune function. INS has been shown to modulate the stress response by reducing the release of stress hormones, such as cortisol, and dampening the activation of the HPA axis. By mitigating the stress response, INS may indirectly contribute to maintaining a balanced H:L in Sonali chickens [14].

Exogenous INS enhanced GLUT12 and IR gene expression

Stress responses are known to markedly influence metabolic processes, including glucose metabolism. Consequently, INS's stress-mitigating effects may be mechanistically associated with its regulatory influence on glucose uptake and metabolism via modulation of gene expression. To examine the effect of exogenous INS on the expression of key genes involved in glucose uptake and metabolism—specifically GLUT12 and IR—Sonali chickens were administered two distinct doses of INS 30 minutes before slaughter. Subsequent analysis of mRNA expression revealed a significant upregulation of GLUT12 in both liver (Fig. 4A) and pancreas (Fig. 4B) tissues following INS administration. Interestingly, GLUT12 expression peaked at a dosage of 4 IU, but significantly declined when the dose was increased to 8 IU. These results suggest that INS not only facilitates GLUT12 translocation to the cell membrane, a well-established function, but also regulates its gene expression. A comparable regulatory pattern was observed for the IR gene in the liver tissue of Sonali chickens, with INS treatment leading to elevated IR transcript levels (Fig. 4C). Furthermore, INS administration stimulated the expression of its own gene (INS) in the pancreas at both 4 and 8 IU doses, with the highest expression recorded at 4 IU (Fig. 4D). This suggests a potential positive feedback mechanism, wherein exogenous INS enhances endogenous INS gene expression.

Collectively, these findings highlight a distinct role of INS in modulating the expression of genes integral to glucose metabolism and uptake, extending beyond its classical metabolic actions. Although limited data exist regarding the influence of INS on GLUT12 and IR gene expression in the liver and pancreas of chickens, insights from studies in other vertebrates provide plausible mechanisms. In mammals, INS is known to regulate glucose metabolism

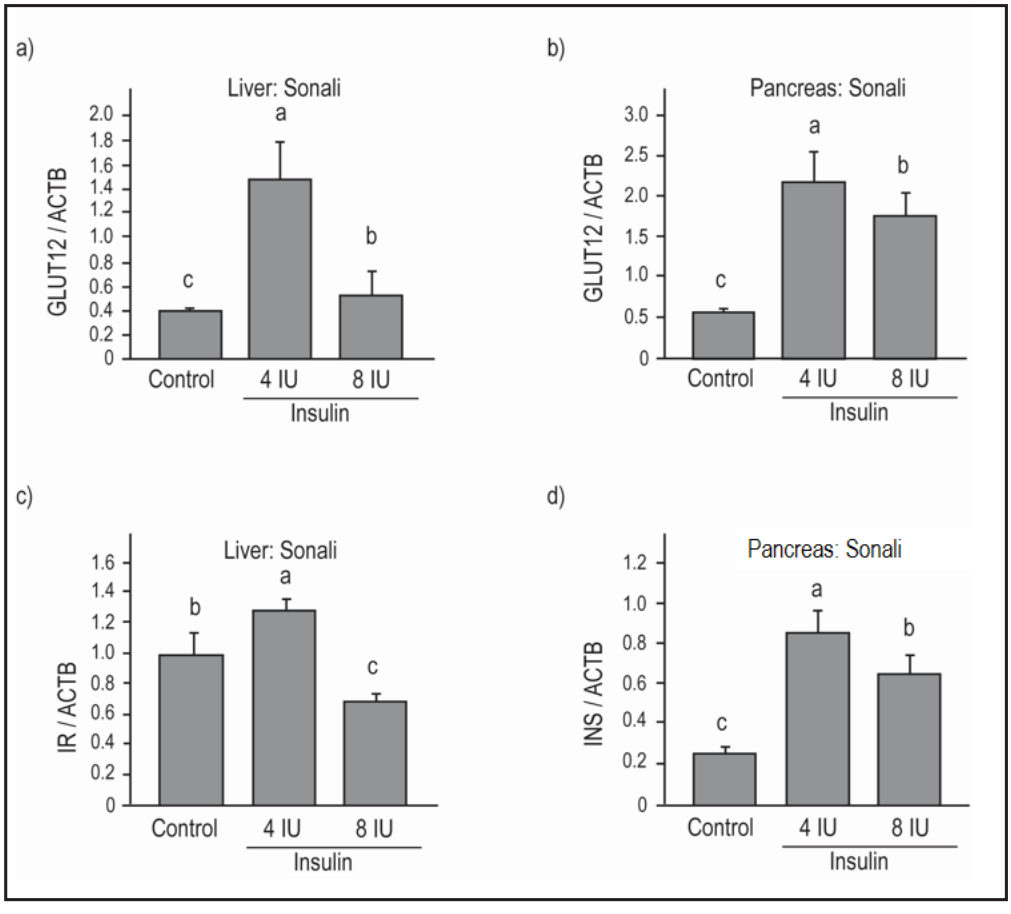

Figure 4. mRNA expression analysis (RT-qPCR) of target genes in Sonali chicken after INS administration. a) Expression of *GLUT12* in liver b) Expression of *GLUT12* in pancreas, c) expression of *IR* in liver and d) Expression of *INS* in liver. Birds were injected subcutaneously with 0, 4, and 8 IU INS and mRNA expressions were measured after 30 minutes of injection. The data represent the mean ± SEM (n = 5), and bars with different superscripts differ significantly.

by upregulating glucose transporter genes such as GLUT2 and GLUT4 in INS-responsive tissues [15].

It is plausible that INS may exert a similar effect on *GLUT12* gene expression in the liver of chickens. INS signaling pathways, such as the phosphoinositide 3-kinase (PI3K)/Akt pathway, may be involved in the regulation of *GLUT12* gene expression by INS [16]. Further investigations are needed to explore the direct impact of INS on the transcriptional regulation of *GLUT12* in the chicken liver.

Exogenous INS interacts with IRs on the surface of liver cells, initiating a cascade of intracellular signaling events. This leads to the activation of downstream signaling molecules, such as insulin receptor substrates (IRSs), PI3K, and protein kinase B (Akt).

The activated signaling pathways result in the activation of transcription factors, such as forkhead box protein O1 and sterol regulatory element-binding protein 1c [17]. These transcription factors bind to specific regions of the insulin receptor gene (INSR) promoter, enhancing its transcription and resulting in increased *IR* mRNA expression.

INS signaling and increased IR expression in liver cells can also trigger feedback mechanisms. This includes the activation of negative feedback loops, such as the phosphorylation and inhibition of IRS proteins, to regulate the intensity and duration of the INS signaling response.

Exogenous INS administration can activate IRs in the pancreatic beta cells. This activation triggers intracellular signaling cascades that lead to the activation of transcription factors, including pancreatic and duodenal homeobox 1 and MafA. These transcription factors bind to specific regions of the INS gene promoter, promoting its transcription and resulting in increased INS mRNA expression [13].

INS itself acts as a key regulator of beta cell function. Exogenous INS administration can provide additional INS to pancreatic beta cells, which can improve their functionality and enhance INS production. This enhanced beta cell function can contribute to increased INS mRNA expression.

Exogenous INS administration helps regulate blood glucose levels. When glucose levels are controlled, it reduces the inhibitory effect of high blood glucose on INS gene expression in the pancreas. This allows for the upregulation of INS mRNA expression in response to exogenous INS administration.

Increased INS levels resulting from exogenous INS administration can trigger negative feedback loops that regulate INS synthesis and secretion. These feedback loops involve the activation of various signaling pathways that can modulate the expression of INS mRNA in the pancreatic beta cells [18].

The HPA axis is involved in the regulation of cortisol production. INS has been shown to inhibit the HPA axis by suppressing the release of corticotropin-releasing hormone from the hypothalamus and adrenocorticotropic hormone (ACTH) from the pituitary gland. This inhibition subsequently reduces the stimulation of cortisol synthesis and secretion by the adrenal glands [19]. INS administration helps regulate blood glucose levels, preventing excessive glucose fluctuations. High blood glucose levels can activate the HPA axis and stimulate cortisol production [20]. By maintaining glucose homeostasis, exogenous INS reduces the need for the HPA axis to respond to glucose dysregulation, leading to decreased cortisol concentration. INS exhibits anti-inflammatory properties, and chronic inflammation can contribute to cortisol release. By reducing inflammation, exogenous INS may indirectly lower cortisol levels. INS and cortisol have complex interactions within the body. INS can inhibit cortisol release by interfering with the enzymatic processes involved in cortisol synthesis or by affecting the sensitivity of adrenal gland receptors to ACTH stimulation.

It is important to note that the proposed mechanisms are speculative and require experimental validation in the context of chicken physiology. Future research employing molecular techniques, such as gene expression analysis, promoter studies, and mechanistic studies of INS signaling pathways in chickens, would provide a more comprehensive understanding of the specific impact of INS on the mRNA expression of *GLUT12* and the INSR in the liver and pancreas, respectively.

Conclusion

INS administration significantly reduced H:L ratios and serum cortisol levels in Sonali chickens, indicating its potential to alleviate slaughter-induced stress. However, in broiler chickens, cortisol levels unexpectedly increased, suggesting strain-specific responses. INS also upregulated GLUT12 and IR gene expression, highlighting its broader role in modulating genes involved in glucose metabolism. These findings suggest that INS may help reduce stress in poultry beyond its metabolic function. While the underlying mechanisms require further investigation, the study indicates that INS could be a promising approach to minimize stress during slaughter in domestic birds.

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Conflict of interest

The authors declare no competing interest.

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