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# The Effects of Central Ghrelin on Serum Parameters Related to Energy Metabolism in Neonatal Chicks

**Ladan Emadi[1*], Hossain Jonaidi[1], Saeed Nazifi[2], Hamed Khasti[1], Elahe Rohani[3], Hiroyuki Kaiya[4]**

1. *Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman (SBUK), Kerman, Iran*
2. *Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Shiraz, Shiraz, Iran*
3. *Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran*
4. *Department of Biochemistry, National Cerebral and Cardiovascular Centre Research Institute, 6-1 Kishibe-Shinmachi, Suita, Osaka, Japan*

## Abstract

**BACKGROUND:** Ghrelin is a regulatory peptide with endocrine and metabolic effects in mammals and birds.

**OBJECTIVES:** The aim of this study was to investigate the possible effects of intracerebroventricular (ICV) injection of ghrelin on the plasma level of some hormones and biochemical indices involved in the energy balance of neonatal chicks.

**METHODS:** Intracerebroventricular injection of 20 or 40 pmol ghrelin/individual was done. Blood samples were collected from the jugular vein 15 and 30 minutes after the ICV injection of ghrelin to measure serum parameters.

**RESULTS:** The ICV administration of 20 and 40 pmol ghrelin/individual had no effects at 15 min post-injection, but at 30 min post-injection, the triiodothyronine (T3) level significantly decreased in a dose-dependent manner. The leptin level also declined significantly compared to that of the control group. There were no significant changes in other parameters, including insulin, T4, triglyceride, cholesterol, and glucose.

**CONCLUSIONS:** It can be concluded that the changes that occurred in T3 and leptin levels may have been due to the effects of ghrelin on the metabolic rate and food intake (concerning T3) and the parallel action of ghrelin and leptin (concerning leptin).

**KEYWORDS:** Central, Energy metabolism, Ghrelin, Neonatal chicks, Serum parameters

## Correspondence

Ladan Emadi, Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman (SBUK),76169-133 Kerman, Iran. Tel: +98 (034) 31322942, Fax: +98 (034) 3325744, Email: emadil@uk.ac.ir

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## Introduction

Ghrelin, an acylated twenty-eight-amino acid orexigenic peptide hormone, was firstly identified in the rat stomach. Ghrelin also exists in various vertebrate species, including birds (Vizcarra, Wright & Vizcarra, 2012), secreted mainly from the proventriculus (Kaiya, Kangawa & Miyazato, 2013). It is involved in various physiological actions, such as regulating pituitary hormones, appetite, food intake, lipid metabolism, and energy expenditure (Abdalla, 2015). Ghrelin in chickens consists of 26 amino acids; this hormone has been identified in numerous bird species, such as chicken, turkey (Ceron-Romero *et al.*, 2021), duck, and Japanese quail (Kaiya *et al.*, 2002; Kaiya *et al.*, 2008).

Evidence revealed that the central administration of ghrelin could stimulate growth hormone (GH) release and food intake in rats. Interestingly, in birds, the central and peripheral administration of either humans' or chicken's ghrelin stimulated the GH release, while its central, but not peripheral, injection strongly inhibited food intake (Tschöp, Smiley & Heiman, 2000; Lin and Sun, 2012; Müller *et al.*, 2015).

It has been documented that ghrelin is expressed in rat-specific cell types of the anterior pituitary gland, such as somatotrophs, lactotrophs, and thyrotrophs. This evidence shows that ghrelin may act in a paracrine-like fashion to regulate the anterior pituitary gland cell function (Caminos *et al.*, 2003). The expression of ghrelin in thyroid C cells and the presence of its receptor in follicular thyroid cells suggest that ghrelin regulates thyroid function in a paracrine manner (Mano-Otagiri *et al.*, 2009). Functional ghrelin receptor (GHS-R1a) was predominantly expressed in the pituitary gland and, at much lower levels, in the thyroid gland, pancreas, spleen, myocardium, and adrenal gland. Ghrelin modulates energy expenditure affecting the Hypothalamus-Hypophysis-Thyroid axis (HPT axis) (Dos-Santos *et al.*, 2019).

Leptin is released from the adipose tissue, where it acts as a signal between the peripheral lipid stores and the central nervous system. Chicken leptin protein contains three cysteine residues containing two cysteine residues in mammals. Leptin is expressed not only in the adipose tissue but also in the liver and plays a significant role in regulating food intake and energy balance. Leptin inhibits food intake both in mammals and birds (Lõhmus *et al.*, 2003). The exogenous administration of (species) leptin decreases the number of orexigenic peptides (anabolic effectors) and increases the anorexigenic peptides (catabolic effectors), resulting in the reduction of food intake. The leptin gene expression is sensitive to hormonal treatment in the liver, where the major source of leptin, but not in the adipose tissue in chickens (Ashwell *et al.*, 1999).

To date, the effects of ghrelin on serum parameters involved in energy hemostasis have not been examined in chicks. The present study was aimed to evaluate the changes in some biochemical serum parameters, such as triiodothyronine (T3), thyroxin (T4), leptin, insulin, glucose, triglyceride, and cholesterol, after the intracerebroventricular (ICV) injection of ghrelin in neonatal chicks.

## Materials and Methods

### Animals

One day-old-male Ross broiler chicks were obtained from Mahan hatchery (Kerman, Iran). House temperature was kept at 30°C, and humidity was controlled at 45-50%. A continuous lighting regimen was provided to the birds throughout the experimental period. The broilers were fed with a commercial basal diet (21% protein and 2,900 kcal metabolizable energy). Diets in mash form and water were provided ad libitum throughout the experimental period.

On the day prior to the injection, the chicks were placed in individual cages, and 6-day-old chicks were selected for ICV injection.

### ICV Injection

Customly synthesized octanoylated chicken ghrelin, with 26 amino acids (GSS (n-octanoyl) FLSPTYKNIQQQKDTRKPTARLH, ASBIO Pharma Co. Ltd., Japan)), was used in this study. Ghrelin was dissolved in 5% mannitol solution to prevent the absorption of peptides to the wall of the tube or syringes, and 0.1% Evans Blue. This solution

was also used as a control. ICV injections were done in a volume of 5 µg by using a microsyringe, as described by Furuse (Furuse *et al.*, 1997), without anesthesia. Briefly, the head of each chick was held with an acrylic device in which the bill holder was 45°, and the calvarium was parallel to the surface of the table. The injection was performed through a hole in the plate overlying the skull immediately over the right lateral ventricle. Then, a microsyringe was inserted into the right lateral ventricle through the hole, and the test solution was injected. The top of the needle was penetrated 3-4 mm below the skull's skin. This procedure appeared not to induce any physiological stress (Saito *et al.*, 2005).

### Experiments

Before each experiment, the birds were weighed and distributed into experimental groups based on their body weight so that the average weight between the treatment groups would be as uniform as possible.

At the end of the experiment, inhalation anesthesia was induced in chicks by exposure to ether gas, and then birds' decapitation was carried out. The correct injection was confirmed by the presence of Evans Blue dye in the lateral ventricle. Birds with no dye trace in the lateral ventricle region were not used for data analysis.

Experiment 1: The chicks were divided into three groups, including six animals. Group 1 (control) included the animals which received 5% mannitol solution with 0.1% Evans Blue. Group 2 and 3 received 20 and 40 pmol ghrelin/individual, respectively. Blood samples were collected from the jugular vein 15 minutes after the ICV injection and transferred to vacuum tubes. Blood samples were then centrifuged, and their serum was obtained and stored at -20°C until serum T3, T4, triglyceride, total cholesterol, glucose, insulin, and leptin were taken.

Experiment 2: The second experiment was similar to the first, except that the blood sample collection was done 30 minutes post-injection.

### Measurement of Biochemical Parameters

Serum T3 and T4 levels were measured using the Iran Padtan-Elm competitive ELISA kit with a minimum sensitivity of 0.5 ng/mL and 0.4 µ g/dL, respectively. The serum leptin and insulin levels were measured using commercial chicken-specific ELISA kits using a quantitative sandwich enzyme immunoassay (Shanghai Crystal Day Biotech, Shanghai, China).

The sensitivity of the insulin kit was 0.59 µIU/mL. The intra- and inter-assay precision of the insulin kit were CV < 15%. The sensitivity of the leptin kit was 0.078 ng/mL. The intra- and inter-assay precision of the leptin kit were CV < 8% and CV < 10%, respectively.

Serum biochemical analyses included glucose, cholesterol, and triglyceride, which were determined using commercial kits (Pars Azmoon Kits, Iran) and a biochemical auto-analyzer (Alpha Classic AT$^{++}$, Sanjesh Company, Iran). All measurements were done based on the instructions provided by the manufacturer regarding the use of kits**.**

### Statistical Analyses

The data were expressed as mean ± SEM. Statistical analysis was performed using a one-way analysis of variance by the general linear modeling procedure. Tukey's multiple range tests used comparisons between the treatment groups. The level of significance was P-value≤0.05.

## Results

In experiment 1, the ICV administration of ghrelin had no significant effects on any of the parameters at 15 minutes after the injection compared to the control group (Table 1). In experiment 2, where blood was collected 30 minutes after the injection, serum T3 level decreased significantly in a dose-dependent manner. Also, serum leptin levels declined significantly compared to that of the control group. Meanwhile, there were no significant changes between the experimental groups with regard to other parameters, including triglyceride, cholesterol, insulin, glucose, and T4 (Table 2).

**Table 1.** Biochemical serum parameters (mean ± SEM) at 15 min after the ICV injection of ghrelin (20 and 40 pmol) in broiler chicks

| | 15 minutes after injection | | | | | | |
|---|---|---|---|---|---|---|---|
| **Groups** | T3 (ng/mL) | T4 (ng/mL) | Glucose (mg/dL) | Triglyceride (mg/dL) | Cholesterol (mg/dL) | Insulin (µIU/mL | Leptin (ng/mL) |
| **Control** | 1.44±0.047 | 9.62±0.3 | 175.75±5.26 | 25.05±1.18 | 182.8±10.84 | 3.59±0.23 | 1.57±0.082 |
| **Ghrelin 20 pmol** | 1.4±0.045 | 9.35±0.26 | 175.73±5.37 | 25.53±1.43 | 189.27±8.34 | 3.35±0.17 | 1.45±0.082 |
| **Ghrelin 40 pmol** | 1.4±0.35 | 9.6±0.25 | 176.17±3.93 | 24.85±0.84 | 179±8.43 | 3.46±0.18 | 1.44±0.063 |

**Table 2.** Biochemical serum parameters (mean ± SEM) at 30 min after the ICV injection of ghrelin (20 and 40 pmol) in broiler chicks

| | 30 minutes after injection | | | | | | |
|---|---|---|---|---|---|---|---|
| **groups** | T3 (ng/mL) | T4 (ng/mL) | Glucose (mg/dL) | Triglyceride (mg/dL) | Cholesterol (mg/dL) | Insulin (µIU/mL) | Leptin (ng/mL) |
| **control** | 1.44±0.054 | 9.59±0.34 | 176.43±4.69 | 24.98±1.13 | 180.86±10.18 | 3.39±0.2 | 1.54±0.082 |
| **Ghrelin 20 pmol** | 1.23±0.031 [a] | 9.19±0.27 | 177.75±4.21 | 25.4±0.91 | 184.75±7.55 | 3.49±0.2 | 1.23±0.059 [a] |
| **Ghrelin 40 pmol** | 1.07±0.028 [ab] | 8.73±0.24 | 178.38±4.43 | 25.37±1.04 | 184.62±7.13 | 3.47±0.2 | 1.04±0.056 [a] |

a: A significant difference was observed in the control group at the 30 minute.
ab: A significant difference was observed in the 20 pmol ghrelin group at the 30 minute.

## Discussion

One of the functional differences between rodents and birds regarding ghrelin is that this peptide enhances the utilization of carbohydrates in rats and mice to promote energy conservation in their fat tissues (Tschöp *et al.*, 2000; Thompson *et al.*, 2004). In contrast, ghrelin reduces the accumulation of fat stores in chickens by the down-regulation of the mRNA level of a lipogenic enzyme, fatty acid synthase (FAS), and its transcription factors in the liver (Buyse *et al.*, 2009). There is a relationship between the amount of subcutaneous fat stores and restlessness during migration in migrating birds. More activity and migratory restlessness seem to be associated with larger fat stores in birds. In this situation, the birds migrate faster and stay shorter at stopovers (Kokkinos *et al.*, 2007; Eikenaar and Schläfke, 2013). There is little doubt that circulating ghrelin concentrations reflect body fat stores. It has been reported that high ghrelin levels reduce the accumulation of fat stores and activate the breakdown of lipids in the liver of fat individuals. This is necessary for migration because fat is the primary fuel for migrating birds (Sjöberg *et al.*, 2015). It may be true that serum ghrelin levels increase at the onset of migration.

It has also been reported that in small rodents, the injection of ghrelin increases blood glucose, reduces glucose tolerance, and restricts insulin secretion via direct action on the pancreatic islets of Langerhans (Caminos *et al.*, 2003). This is not in agreement with the present study's findings because no changes were observed in the serum levels of glucose and insulin in the neonatal chicks in the present study. Previous reports have shown that the central and subcutaneous administration of ghrelin or GHS injection increases the respiratory quotient (RQ), decreases fat oxidation, increases the expression of fat-storage enzymes in white adipose tissue, and induces weight gain in rodents (Tschöp *et al.*, 2000; Tschöp *et al.*, 2002;

Theander-Carrillo *et al.*, 2006). In contrast, peripheral ghrelin administration significantly decreased the RQ values for up to 14 h in one-week-old broiler chickens (Tschöp *et al.*, 2000; Tschöp *et al.*, 2002). Similar to our findings, ghrelin had no effect on the levels of plasma glucose and triglyceride in small rodents, when injected peripherally (Tschöp *et al.*, 2000; Tschöp *et al.*, 2002).

Leptin, which is an anorexigenic hormone that is produced by white adipose tissue, decreases food intake and energy expenditure by the direct activation of POMC/CART neurons and inhibition of NPY-/AgRP neurons, resulting in a reduction in body weight. Central infusion of leptin agonists has been shown to have a beneficial effect on glucose homeostasis, as leptin infusion can decrease abdominal fat, increase insulin sensitivity, and decrease hepatic glucose production (Tschöp *et al.*, 2000). Blood leptin levels are positively correlated with adiposity. Therefore, leptin may be considered an indicator reflecting body energy stores, which link fat deposits to the central nervous system. It has been shown that leptin expression in chickens, as in mammals, is regulated by hormonal and nutritional status (Lin & Sun, 2012). The blood leptin levels are regulated by the nutritional state, with high levels in the fed state compared to the fasted state in chickens.

ccording to the literature, enhancing the circulating GH in chickens can depress food intake (Mano-Otagiri *et al.*, 2009). In chickens, chronic GH infusion increases leptin expression in the liver but not in the adipose tissue (Kokkinos *et al.*, 2007). GH has a direct effect on leptin is not concomitant with a decrease in food intake. Avian adipose tissue seems to be refractory to insulin, dexamethasone, and GH. This absence of adipose tissue responsiveness may be explained by a constitutive leptin expression in this tissue and/or by the role of adipose tissue, which is considered as a storage site versus the liver as the primary site of lipogenesis, in avian species. Thus, it can be concluded that the reduction of leptin observed in the present study may be due to ghrelin-induced food inhibition and/or the direct effect of ghrelin on the liver.

It is worth noting that the leptin administration did not affect agouti-related peptide (AGRP) and proopiomelanocortin (POMC), orexigenic, and anorexigenic peptides that are expressed in the hypothalamic arcuate nucleus and corticotrophin-releasing hormone (CRH), an anorexigenic/catabolic neuropeptide which is expressed in the hypothalamic paraventricular nucleus, respectively, in neonatal chicks. Also, it must be added that the effects of AGRP were not the same on different strains of chicken; it stimulated food intake in the layer but not in the broiler chicks (Tachibana *et al.*, 2001).

It has been shown that fasting and a β3-adrenoreceptor agonist suppress the synthesis of leptin in rodents and humans (Koutkia *et al.*, 2003). It has also been demonstrated that the central administration of ghrelin suppresses the activity of the sympathetic nerve of the brown adipose tissue (BAT) in rats. It is noteworthy that ghrelin induces hypophagia via a β2-adrenergic receptor in chickens (Zendehdel & Hassanpour, 2014). Based on these findings, the reduced serum level of leptin in the present investigation could be attributed to the effects of ghrelin on the sympathetic system in chicks

The activation of the Hypothalamic-Pituitary-Thyroid (HPT) axis stimulates the metabolic rate of some tissues such as liver, heart, muscle, and adipose tissue, thereby increasing thermogenesis and energy expenditure (Mano-Otagiri *et al.*, 2009; Kaiya, Miyazato & Kangawa, 2011). The ICV injection of ghrelin decreased the activity of the HPT axis in rats; as a result, the thyrotrophic cells in the anterior pituitary became smaller, the TSH plasma level was lower, the thyroid follicles were less active, and the thyroxin (T4) plasma level was reduced (Tachibana *et al.*, 2006). This result is in agreement with that of the present study, in which it was observed that ghrelin reduced the HPT function in chicks by reducing the T3 serum level. This is the first observation of the effect in birds. In vitro investigations have shown that ghrelin increases the TSH-induced proliferation of rat thyrocytes (Lin & Sun, 2012). Although it was initially reported that the elevation of thyroid hormones in humans was induced by the ghrelin action on the thyroid gland, where the ghrelin receptor has been identified to be present. Subsequent studies showed that ghrelin did not change plasma TSH level either in dogs or humans (St-Pierre *et al.*, 2004; Bhatti *et al.*, 2006). These findings suggest that ghrelin may act through the binding sites, which are different from the GHS-R detected in the human thyroid gland (Tachibana *et al.*, 2006;

Dos-Santos *et al.*, 2019). It appears that there is a correlation between thyroid functional status and ghrelin plasma level. To support this hypothesis, it was observed that plasma ghrelin levels decreased and increased in hyperthyroid and hypothyroid rats, respectively (Caminos *et al.*, 2002). Thus, increased food intake in hyperthyroid rats can be regulated through other pathways, which in turn, can inhibit the release of ghrelin. In such situation, the changes in the ghrelin level which correlate to the thyroid function state could reflect a transition to a more energy-efficient metabolic state, finally leading to a positive energy balance (Inoue *et al.*, 2013).

In some studies, it was observed that the leptin infusion decreased the plasma T3 and glucose levels in chickens as a consequence of lowered food intake (Dridi *et al.*, 2005; Theander-Carrillo *et al.*, 2006). Ghrelin induces the release of glucocorticoids both in chickens and mammals (Inoue *et al.*, 2013). In chickens, GH and glucocorticoids are involved in the generation of the active thyroid hormone triiodothyronine (T3); glucocorticoids are also involved in the production of T3 via the up-regulation of type II deiodinase enzyme in the brain (Kühn *et al.*, 2005). The intravenous injection of GH in chickens resulted in an increased T3 plasma concentration during the post-hatch growth period (Inoue *et al.*, 2013) Therefore, it can be stated that ghrelin, due to its GH-releasing effect, may also influence the thyroid function. However, the results of the present study show a decrease in T3, which is the opposite result. We don't know at present why this is the case.

## Conclusion

In conclusion, based on the results of this study, it can be concluded that increased ghrelin levels in the brain of chicks can lead to a reduction in the plasma level of leptin. Neither the physiological importance nor the underlying mechanism of this effect is clear yet. However, this function of ghrelin can be attributed to its inhibitory effect on food intake and/or its direct effect on the liver. Furthermore, the influence of central ghrelin on the sympathetic system may interfere with its action on the leptin secretion. However, as observed in small rodents, the central ghrelin reduced the serum T3 level in chickens in this study, and this effect of ghrelin may be related to its influence on food intake and the metabolic function.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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# اثرات گرلین مرکزی بر پارامترهای سرمی مرتبط با متابولیسم انرژی در جوجه‌های نوزاد

**لادن عمادی*[۱]، حسین جنیدی[۱]، سعید نظیفی[۲]، حامد خواستی[۱]، الهه روحانی[۳]، هیروکی کایا[۴]**

[۱] گروه علوم پایه، دانشکده دامپزشکی، دانشگاه شهید باهنر کرمان، کرمان، ایران

[۲] گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه شیراز، شیراز، ایران

[۳] مرکز تحقیقات علوم اعصاب، موسسه نوروفارماکولوژی، دانشگاه علوم پزشکی کرمان، کرمان، ایران

[۴] گروه بیوشیمی، موسسه مرکزی تحقیقات مغزی و قلبی-عروقی ملی، اوساکا، ژاپن

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**زمینه مطالعه:** گرلین پپتید تنظیمی است که اثرات اندوکرینی و متابولیک در پستانداران و پرندگان دارد.

**هدف:** هدف از این مطالعه بررسی اثرات احتمالی تزریق درون بطن مغزی گرلین بر میزان پلاسمایی برخی هورمون‌ها و شاخص‌های بیوشیمیایی درگیر در بالانس انرژی جوجه‌های نوزاد است.

**روش کار:** تجویز درون بطن مغزی ۲۰ یا ۴۰ پیکو مول گرلین به ازاء هر قطعه جوجه انجام شد و نمونهٔ خون از سیاهرگ وداج، ۱۵ و ۳۰ دقیقه پس از تزریق درون بطن مغزی گرلین برای اندازه‌گیری پارامترهای سرمی جمع‌آوری گردید.

**نتایج:** جوجه تجویز درون بطن مغزی ۲۰ و ۴۰ پیکومول گرلین به جوجه، ۱۵ دقیقه پس از تزریق تاثیری نداشته، اما ۳۰ دقیقه پس از تزریق سبب کاهش معنادار میزان تری یدوتیرونین به‌صورت وابسته به دوز شد. همچنین میزان لپتین به‌طور معنادار در مقایسه با گروه کنترل کاهش یافت. تغییر معناداری در سایر پارامترها، شامل انسولین، تیروکسین، تری‌گلیسرید، کلسترول و گلوکز وجود نداشت.

**نتیجه‌گیری نهایی:** چنین نتیجه‌گیری می‌شود که تغییرات رخ داده در میزان تری یدوتیرونین و لپتین ممکن است در نتیجه تاثیرات گرلین بر میزان متابولیسم و میزان اخذ غذا (در نتیجه اثر تری یدوتیرونین) و فعالیت موازی گرلین و لپتین (با توجه به اثر لپتین) باشد.

**واژه‌های کلیدی:** مرکزی، متابولیسم انرژی، گرلین، جوجه‌های نوزاد، پارامترهای سرمی

**نویسندهٔ مسئول:** لادن عمادی ، گروه علوم پایه دانشکده دامپزشکی، دانشگاه شهید باهنر کرمان، کرمان، ایران ایمیل:emadil@uk.ac.ir