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Central and peripheral administrations of insulin-like growth factor-1 suppress food intake in chicks

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ABSTRACT

A number of studies have been made on the physiological actions of insulin-like growth factor-1 (IGF-1) in mammals and birds. In mammals, the effects of central administration of IGF-1 on food intake have been examined. For example, intracerebroventricular administration of IGF-1 significantly decreased food intake in diabetic rats, but not in sheep and nondiabetic rats. The chicken is known to be a hyperglycemic animal. Like satiety hormones, plasma IGF-1 levels are elevated postprandially in chickens. In this study, we hypothesized that IGF-1 is involved in the regulation of food intake in chickens. Intracerebroventricular administration of IGF-1 significantly suppressed food intake in chicks in a dose dependent manner. Both the mRNAs of IGF-1 and its receptor were expressed throughout the brain. However, the mRNA levels of IGF-1 were not influenced by fasting and refeeding in all regions of the brain. On the other hand, 6 h of fasting significantly suppressed mRNA expression of hepatic IGF-1, and this effect was significantly reversed by 6 h of refeeding. Furthermore, intravascular administration of IGF-1 significantly suppressed food intake in chicks. These findings suggest that IGF-1 may function as a satiety hormone in chickens.

1. Introduction

Physiological and molecular mechanisms involved in the regulation of food intake in chickens have been investigated in recent decades [14,32]. Lines of evidence suggest that physiological roles of several peripheral hormones differ between mammals and chickens. For example, the adipocytokine leptin and gut hormones play important roles in appetite regulation in mammals [39]. However, leptin is densely expressed in the brain but not in the adipose tissue in chickens [35]. Several gut hormones, such as cholecystokinin [14], glucagon-like peptide-2 [16], and peptide YY [1], suppress food intake in chickens when administered peripherally, but the physiological importance of these hormones have not yet been elucidated [14].

Over the past decades, a number of studies have been made on the physiological actions of insulin-like growth factor-1 (IGF-1) in peripheral tissues and the central nervous system. For example, IGF-1 is a key regulator of muscle development and metabolism in mammals and birds [7,8]. Holzenberger et al. suggested the involvement of the IGF system in neurogenesis and differentiation, and possibly in neural plasticity and learning in mammals and birds [12]. In mammals, the effects of central administration of IGF-1 on food intake are controversial. Intracerebroventricular administration of IGF-1 did not influence food intake in sheep [10] but significantly increased food intake in rats [34]. However, intracerebroventricular administration of IGF-1 significantly decreased food intake in diabetic rats [21]. Lines of evidence demonstrate that IGF-1 crosses the blood-brain barrier [2,28,31]. Therefore, it is possible that central or peripheral IGF-1 is involved in the appetite regulatory system of mammals, although the physiological roles are different depending on the physiological conditions or species.

The effects of IGF-1 are similar to those of insulin in many aspects in chickens [9,36,37,40]. We previously reported that central administration of insulin suppresses food intake in chicks [13]. However, the effects of IGF-1 on food intake has not yet been examined in chickens. IGF-1 and its receptor are expressed in the brain [12], and plasma IGF-1 levels are elevated postprandially [18]. Postprandial elevation of appetite suppressive hormones is sensed by the brain as a satiety signal in mammals and birds [14,39]. These findings raise the hypothesis that IGF-1 is also involved in the regulation of food intake in the central nervous system and/or peripheral circulation in chickens.

In this study, we investigated the possible involvement of IGF-1 in the mechanism of food intake regulation in chicks. The results provide

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direct evidence that IGF-1 suppresses food intake in chicks.

2. Materials and methods

2.1. Animals and peptides

Day-old male chicks (Ross 308) were purchased from a local hatchery (Ishii Co., Ltd., Tokushima, Japan). They were given free access to water and a commercial chick starter diet (Nippon Formula Feed Mfg. Co., Ltd., Kanagawa, Japan). This study was approved by the Institutional Animal Care and Use Committee and carried out according to the Kobe University Animal Experimentation Regulation. Human IGF-1 was purchased from Novus Biologicals, LLC (Co, USA).

2.2. Experiment 1: effects of central administration of IGF-1 on food intake chicks

Fourty-eight 8-day-old chicks were weighed and allocated to four groups based on body weight (12 birds in each group). IGF-1 was dissolved in 0.85% (w/v) saline solution containing 0.1% (w/v) Evans Blue. The peptide was intracerebroventricularly administered according to the method of Davis et al. [6] at a volume of 10 μL. Chicks were administered IGF-1 (0, 30, 100, or 300 pmol). Food intake was measured at 30, 60, and 120 min after administration. At the end of the experiment, the chicks were euthanized by decapitation. Verification of injection was made by observation of the presence of Evans Blue dye in the lateral ventricle.

2.3. Experiment 2: real-time PCR analysis of IGF-1 and its receptor mRNA in the chicken brain

Four 7-day-old chicks were euthanized by decapitation. The whole brains were collected and preserved in RNAlater® tissue storage reagent (Sigma-Aldrich Co., St. Louis, MO, USA) and divided into six regions (telencephalon, optic lobes, cerebellum, rostral part of the brainstem, middle part of the brainstem, and caudal part of the brainstem) as described previously [1]. Total RNA extraction and cDNA synthesis were performed using the Sepazol-RNA I (Nacalai Tesque, Inc., Kyoto, Japan) and ReverTra Ace® qPCR RT Master Mix with gDNA Remover (Toyobo Co., Ltd., Osaka, Japan) as described previously [15]. The cDNA of the chicken IGF-1 (GenBank accession number: NM_001004384) and IGF-1 receptor (GenBank accession number: NM_205032) were amplified with the following primers: IGF-1 sense, 5′-GCT GCC GGC CCA GAA-3′; IGF-1 antisense, 5′-ACG AAC TGA AGA GCA TCA ACC A-3′; IGF-1R sense, 5′-GGA GAA TTT CAT GGG TCT GAT TG-3′; IGF-1R antisense, 5′-CAT GGG AAT GGC GAA TCT TC-3′. Complementary DNA of ribosomal protein S17 (GenBank accession number: NM_204217) as an internal standard was amplified with primers as described previously [16]. Messenger RNA levels were quantified in duplicate using an Applied Biosystems 7300 Real-Time PCR system and SYBR® Premix Ex Taq™ II (Tli RNaseH Plus) (Takara Bio Inc., Shiga, Japan) according to the supplier's recommendations. The thermal cycle was as follows: 1 cycle at 95 °C for 30 s, and 40 cycles at 95 °C for 5 s and 60 °C for 31 s. After the reactions, the specificity of amplifications in each sample was confirmed by dissociation analysis showing that each sample gave a single melting peak. Relative gene expression was calculated by comparing the number of thermal cycles that were necessary to generate threshold amounts of product (CT). CT was calculated for the target gene and for RPS17. For each cDNA sample, the CT for RPS17 was subtracted from the CT for the target gene to give the parameter ΔCT, thus normalizing the initial amount of RNA used. The amount of target gene mRNA was calculated as $2^{-\Delta\Delta CT}$, where ΔΔCT is the difference between the ΔCT of the two cDNA samples to be compared.

2.4. Experiment 3: effects of fasting and refeeding on IGF-1 mRNA levels in the brain of chicks

Eighteen 8-day-old chicks were weighed, allocated based on body weight, and euthanized by decapitation after 0, 6 h of fasting, or 6 h of refeeding after 6 h of fasting. The whole brains were collected, and the mRNA levels of IGF-1 were quantified as described in Experiment 2.

2.5. Experiment 4: effects of fasting and refeeding on hepatic IGF-1 mRNA levels in chicks

Eighteen 8-day-old chicks were weighed, allocated based on body weight, and euthanized by decapitation after 0, 6 h of fasting, or 6 h of refeeding after 6 h of fasting. The liver was excised, weighed, and frozen immediately by liquid nitrogen, and stored at −80 °C. The mRNA levels of IGF-1 were quantified as described in Experiment 2.

2.6. Experiment 5: effects of peripheral administration of IGF-1 on food intake in chicks

Thirty six 8-day-old chicks were weighed and allocated to three groups based on body weight (12 birds in each group). IGF-1 was dissolved in a 0.85% (w/v) saline solution. The peptide (0, 3, or 12 nmol/mL/kg body weight) was administered via a wing vein with ad libitum feeding. Food intake was measured at 30, 60, and 120 min after administration.

2.7. Data analysis

Data were analyzed by the Tukey-Kramer test. All statistical analyses were performed using the commercial package (StatView version 5, SAS Institute, Cary, NC, USA, 1998).

3. Results

In the present study, we firstly examined the effect of central administration of IGF-1 on food intake in chicks. Intracerebroventricular administration of IGF-1 significantly suppressed food intake in a dose-dependent manner, suggesting that IGF-1 might function as an anorexigenic peptide in the brain (Fig. 1).

In order to evaluate the possible role of brain IGF-1, we next examined the mRNA levels of IGF-1 and the receptor in the brain. Both the mRNAs of IGF-1 and the receptor were expressed throughout the brain

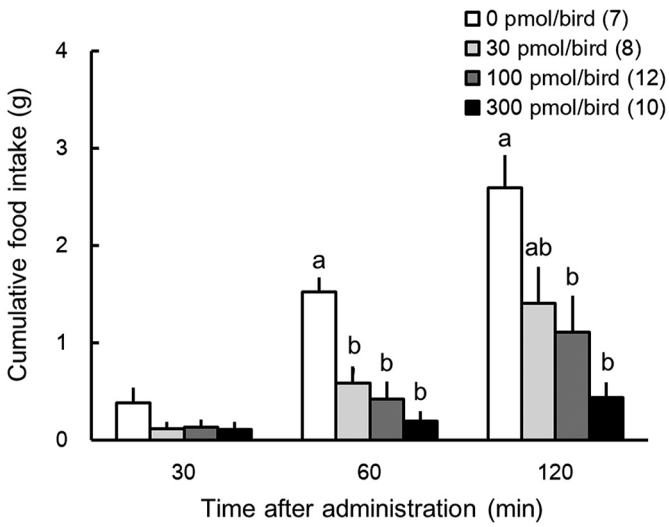

Fig. 1. Effects of central administration of insulin-like growth factor-1 on food intake in chicks. Data represent means ± S.E.M. The number of chicks used is shown in parentheses. Groups with different letters are significantly different ($P < 0.05$).