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

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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.

**Keywords:** appetite, brain, chicken, feed intake, insulin-like growth factor-1, liver

## 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 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 hours of fasting, or 6 hours of refeeding after 6 hours 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 hours of fasting, or 6 hours of refeeding after 6 hours 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. 2). The mRNA level of IGF-1 was significantly higher in the optic lobes than in the rostral part of the brainstem and cerebellum (Fig. 2). On the other hand, the mRNA level of IGF-1R was significantly lower in the telencephalon than in the rostral part of the brainstem, caudal part of the brainstem, and optic lobes. However, fasting and refeeding did not influence the mRNA levels of IGF-1 in all regions of the brain (Fig.3). It is therefore possible that brain IGF-1 is not involved in the regulation of food intake in chickens.

It is well known that liver secretes IGF-1 into the bloodstream in chickens [23]. Therefore, in order to evaluate the possible role of hepatic IGF-1, we next examined the effects of fasting and refeeding on the mRNA levels of IGF-1 in the liver. Six hours of fasting significantly decreased the mRNA levels of hepatic IGF-1, and this effect was significantly reversed by 6 h of refeeding (Fig. 4). Furthermore, we finally examined the effect of peripheral administration of IGF-1 on food intake in chicks and found that intravascular administration of IGF-1 significantly suppressed food intake at 30 and 60 min after administration (Fig. 5). These findings suggest that IGF-1 may function as an postprandial satiety hormone in the peripheral circulation in chickens.

## 4. **Discussion**

The anorexigenic action of IGF-1 was observed in chicks (Fig. 1) and diabetic rats [21] but not in non-diabetic mammals [10, 34]. Birds maintain higher plasma glucose concentrations than other vertebrates of similar body mass [4]. These findings raise the hypothesis that IGF-1 functions as an anorexigenic hormone only in hyperglycemic animals. Radhakrishnan et al. reported that hyperglycemia alters responsiveness to IGF-I, resulting in increased Src homology 2

domain-containing protein-tyrosine phosphatase substrate-1 phosphorylation and assembly of a signaling complex that enhances mitogen-activated protein kinase and phosphatidylinositol 3-kinase (PI3K) pathways [30]. There is evidence that insulin suppresses food intake via the PI3K pathway in mammals [26, 27]. It is therefore possible that IGF-1 suppresses food intake via PI3K pathway in diabetic mammals and birds.

Kita et al. reported that postprandial elevation of hepatic IGF-1 mRNA in egg type chickens at 6 weeks of age [18]. However, the response of hepatic IGF-1 production might be different between strains or age. In fact, IGF-I mRNA was undetectable in the liver of the developing embryo, but during post-hatching development, hepatic IGF-I mRNA levels increased until 4 weeks of age [5]. Several studies demonstrated that plasma IGF-1 levels are different between strains of chickens [17, 19, 29]. Therefore, we have evaluated the effects of fasting and refeeding on hepatic IGF-1 mRNA levels in neonatal chicks and suggested that hepatic IGF-1 production is stimulated by feed intake. Thus, our findings give a new insight into the physiological importance of hepatic IGF-1 in the regulation of food intake in chicks during early post-hatch period.

In the present study, intravascular administration of IGF-1 suppressed food intake in chicks (Fig. 5). Meanwhile, refeeding increased the mRNA levels of IGF-1 in the liver (Fig. 4). There is evidence that the blood IGF-1 level is elevated by food intake in chickens [18]. Fasting, restricted feeding, and low protein diet feeding significantly reduce blood IGF-1 levels in chickens [8]. In mammals, dietary protein elevated blood IGF-1 levels [20]. Therefore, dietary nutrients and/or protein stimulate blood IGF-1 levels, which in turn results in satiety in chickens.

As shown in Figs. 3 and 4, fasting decreased the mRNA levels of IGF-1 in the liver, but not in the brain. Lu et al. reported that a significant increase in the plasma IGF-I level was observed after hatching for each day up to 21 days of age [21]. Burnside and Cogburn reported that during post-hatching development, the plasma IGF-I profile coincided with the expression of hepatic IGF-I mRNA: plasma IGF-I and hepatic IGF-I mRNA levels increased rapidly until a

peak was reached at 4 weeks of age [5]. On the other hand, Holzenberger and Lapointe reported that IGF-I expression in the chicken brain is down-regulated shortly after hatching, and the levels were below detectability at 30 days of age [12]. All these findings suggest that physiological roles of brain IGF-1 differ from those of hepatic IGF-1 in chickens.

Holzenberger and Lapointe suggested that the involvement of the IGF system in neurogenesis and differentiation, and possibly in neural plasticity and learning, may have arisen early in tetrapode/vertebrate evolution [12]. Therefore, IGF-1 and its receptor mRNAs may be widely distributed in the brain of chicks (Fig. 2). Interestingly, the mRNA level of IGF-1 was significantly high in the optic lobes, which are well developed in birds. In probably most avian species the majority of retinal ganglion cells project to the optic tectum, and the tectum projects bilaterally to the thalami nucleus rotundus, which itself sends fibers to the ipsilateral ectostriatum [11]. It is therefore possible that visual information is transmitted via IGF-1 in the optic lobes in chicks.

Foster et al reported that intracerebroventricular administration of IGF-1 does not influence serum IGF-1 levels in sheep [10]. Therefore, it seems likely that central administration of IGF-1 in chicks might not influence blood IGF-1 levels. McMurtry et al. demonstrated that exogenous IGF is present in the free or binding (45 kDa or 150 kDa) form in the blood of chickens when administered peripherally, but most injected IGF-1 apparently abolished 2 h after administration [24]. Therefore, exogenous IGF-1 and its anorexigenic effect probably abolished at 120 min after administration (Fig. 5). Further studies are needed to clarify the relationships between the circulating forms or levels of plasma IGF-1 and the appetite suppressive effect of IGF-1 in chicks.

In the present study, we used human IGF-1 instead of chicken IGF-1. Complete amino acid sequencing of IGF-I purified from chicken plasma established the presence of eight amino acid substitutions compared with human [3]. However, Upton et al. reported that recombinant chicken IGF-I was equipotent with human IGF-I in cell culture bioassays of protein synthesis and

breakdown using rat L6 myoblasts and chick embryo fibroblasts [38]. They also showed that binding of radiolabelled chicken IGF-I and human IGF-I was equivalent in the two cell lines, as was their binding in ligand blots of chicken, sheep and human plasma. In addition, the metabolic clearance of chicken IGF-1 and human IGF-1 was similar when administered intravascularly in 7-week-old chickens [24]. Human IGF-I is frequently used for IGF-1 study in chickens [22, 25, 33, 40]. Therefore, chicken IGF-1 and human IGF-1 probably show similar effects on food intake when administered centrally and peripherally.

## 5. Conclusion

In the present study, we found that central and peripheral administration of IGF-1 suppressed food intake in chicks. We also showed that hepatic IGF-1 mRNA levels were significantly increased in response to feeding. These findings suggest that IGF-1 may function as a satiety hormone in chicks.


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354
355 **Figure captions**
356 Fig. 1. Effects of central administration of insulin-like growth factor-1 on food intake in chicks.
357 Data represent means ± S.E.M. The number of chicks used is shown in parentheses. Groups with
358 different letters are significantly different ($P < 0.05$).
359
360 Fig. 2. Distribution of insulin-like growth factor-1 (IGF-1) and its receptor (IGF-1R) mRNAs in
361 the brain of chicks. Data represent means ± SEM (n = 4). Groups with different letters are
362 significantly different ($P < 0.05$).
363
364 Fig. 3. Effects of fasting and refeeding on the mRNA levels of insulin-like growth factor-1 in
365 the brain. Data are means ± S.E.M. (n = 6).
366
367 Fig. 4. Effects of fasting and refeeding on the hepatic insulin-like growth factor-1 mRNA levels
368 in chicks. Data are means ± S.E.M. (n = 6). Groups with different letters are significantly different
369 ($P < 0.05$).
370
371 Fig. 5. Effects of peripheral administration of insulin-like growth factor-1 on food intake in
372 chicks. Data represent means ± S.E.M. (n = 6). Groups with different letters are significantly
373 different ($P < 0.05$).

Fig. 1

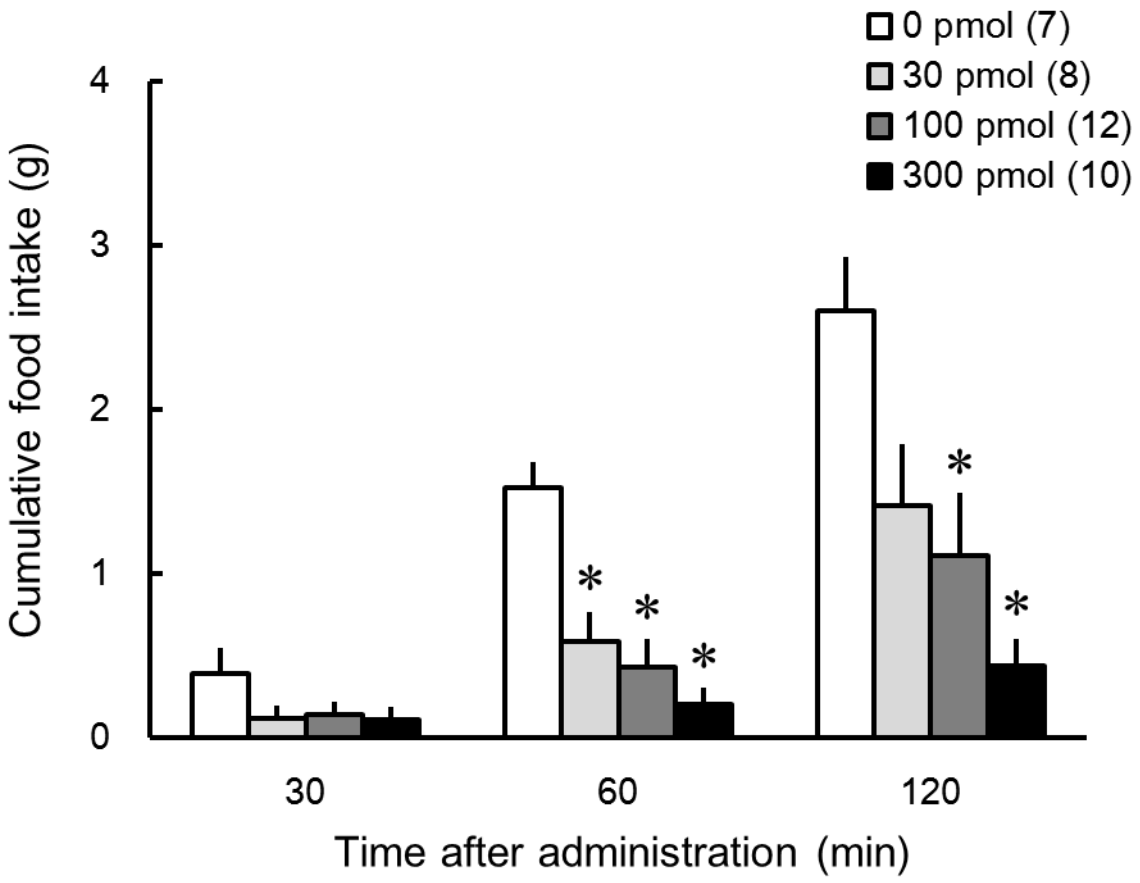
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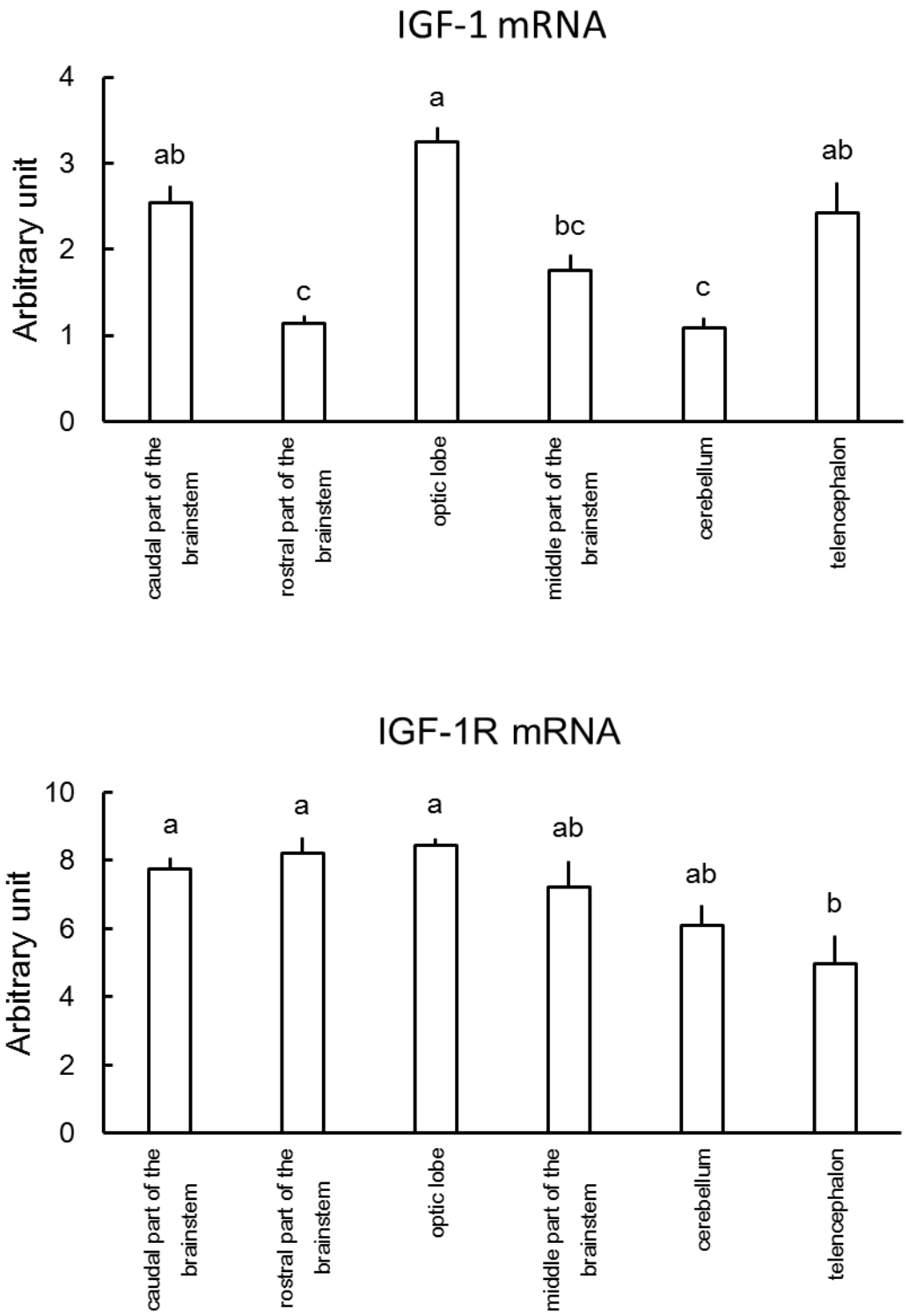
Fig. 2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optic lobe
middle part of the brainstem
cerebellum
telencephalon
IGF-1R mRNA
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a
a
ab
ab
b
caudal part of the brainstem
rostral part of the brainstem
optic lobe
middle part of the brainstem
cerebellum
telencephalon

Fig. 3

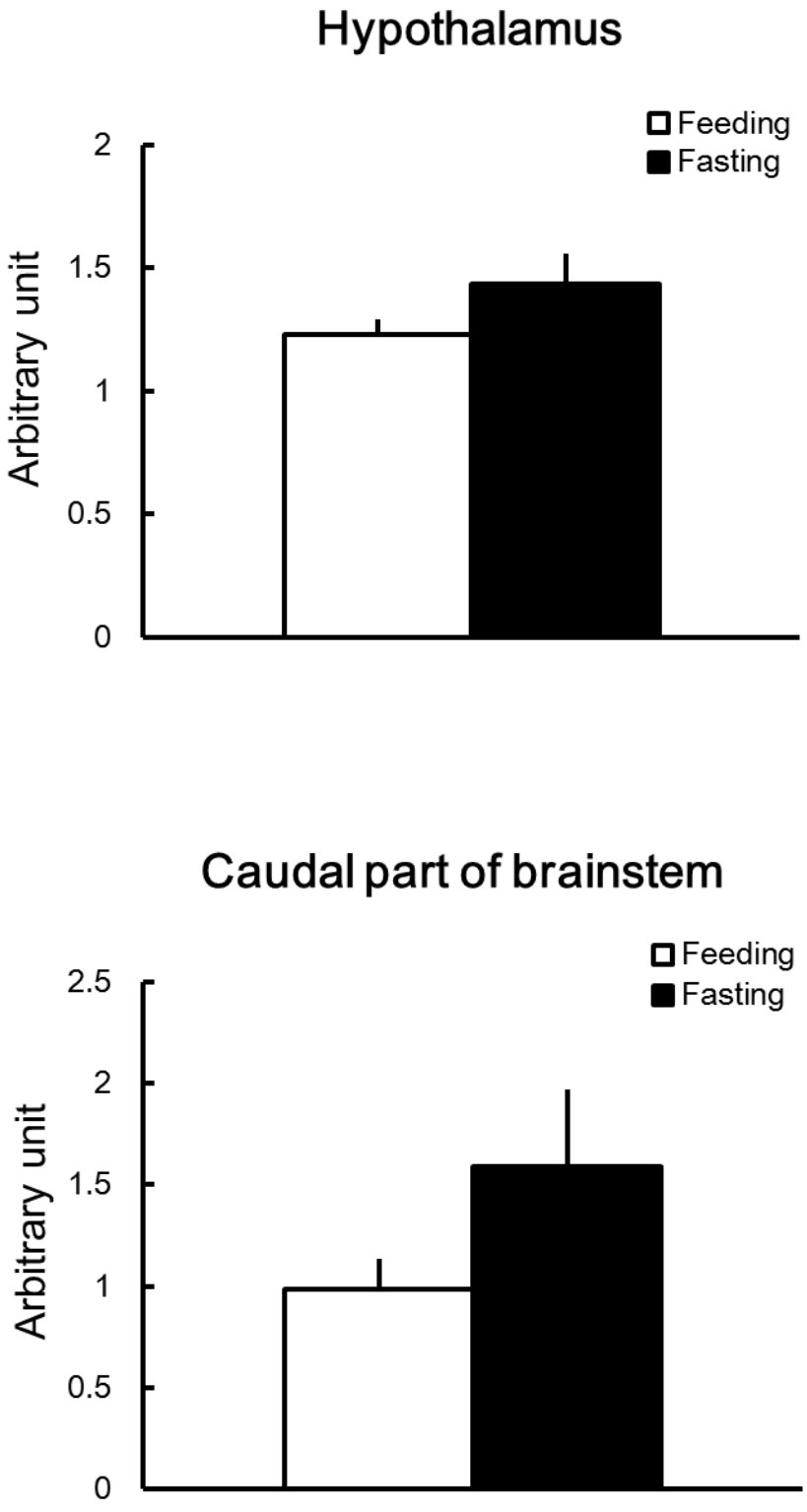

Hypothalamus
Feeding
Fasting
Arbitrary unit
2
1.5
1
0.5
0
Caudal part of brainstem
Feeding
Fasting
Arbitrary unit
2.5
2
1.5
1
0.5
0

Fig. 4

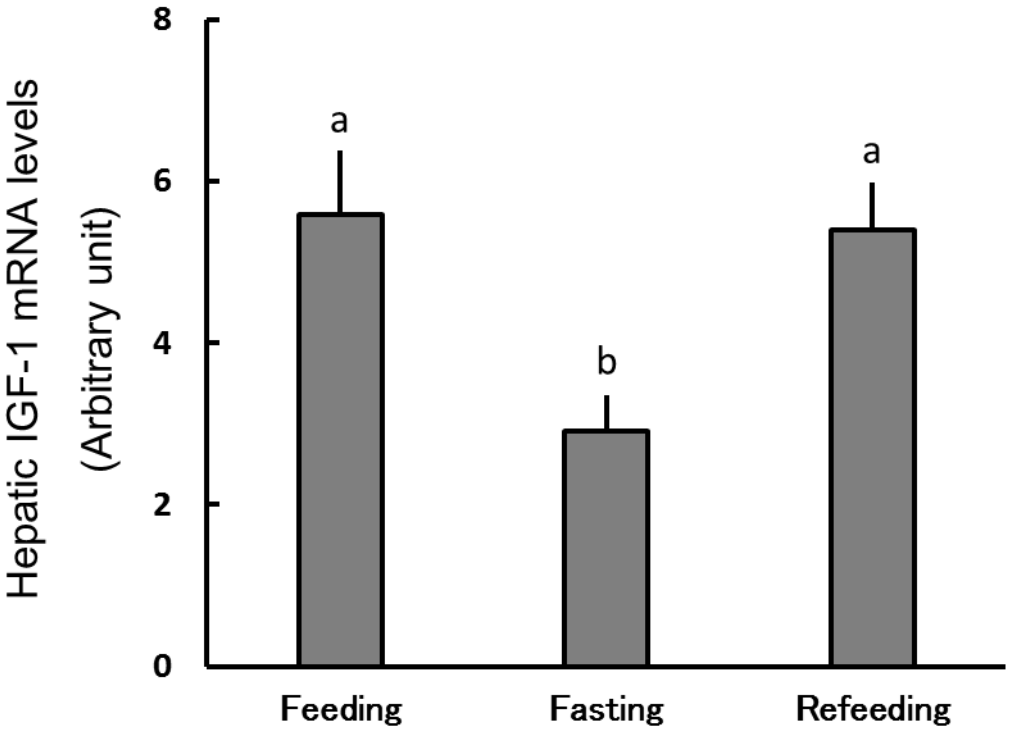
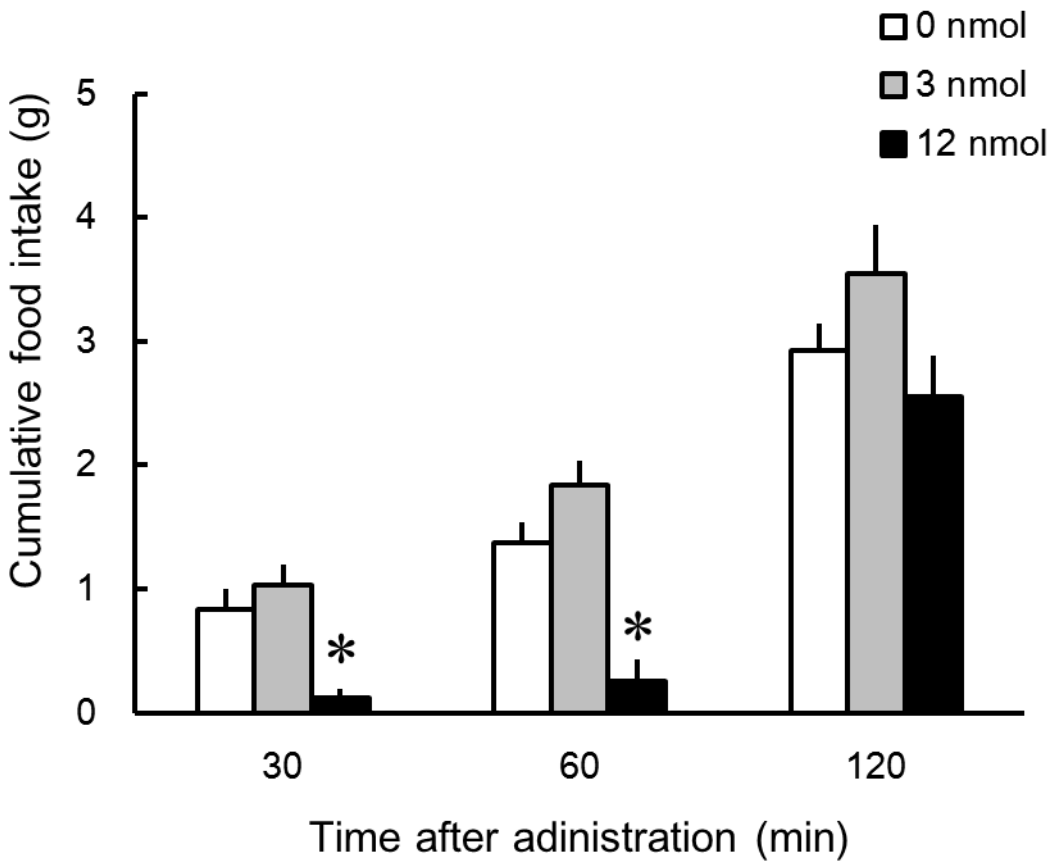

Hepatic IGF-1 mRNA levels
(Arbitrary unit)
8
6
4
2
0
a
b
a
Feeding
Fasting
Refeeding

Fig. 5


0 nmol
3 nmol
12 nmol
Cumulative food intake (g)
0
1
2
3
4
5
*
*
30
60
120
Time after adinistration (min)