Muscle Protein Synthesis Rate Is Altered in Response to a Single Injection of Insulin-like Growth Factor-I in Seven-Day-Old Leghorn Chicks

M. A. Conlon[1,2] and K. Kita

Laboratory of Animal Nutrition, School of Agricultural Sciences, Nagoya University, Nagoya 4648601, Japan

ABSTRACT To determine if a single injection of insulin-like growth factor-I (IGF-I) can affect muscle protein synthesis in chickens, 7-d-old male Single Comb White Leghorn chicks were injected s.c. with physiological saline (control) or 35 μg of recombinant human IGF-I. After 2 h 30 min, or 6, 12, or 24 h the chicks were injected with ^{3}H-phenylalanine and killed, and the fractional synthesis rate (K*s*) of breast muscle protein was measured. The K*s* of IGF-I-treated birds were lower ($P = 0.03$) than controls at 2 h 30 min post-injection, higher ($P = 0.07$) than controls at 6 h post-injection, but not different from controls at later times. A second experiment examined serum changes during the 6 h after chicks were injected with IGF-I or saline as in the first experiment. Serum IGF-I concentration increased relative to almost undetectable levels (1 ng/mL) of controls to 216 ± 59 ng/mL at 20 min after IGF-I injection ($P < 0.001$) and decreased to 12 ± 6 ng/mL by 6 h. Serum glucose and nonprotein nitrogen concentrations were significantly decreased for all or most of the 3 h after IGF-I injection, respectively, but only glucose concentration was the same as controls by 6 h. Low serum glucose and nonprotein nitrogen during the first few hours after IGF-I injection may contribute to the inhibition of Ks at 2.5 h, but the mechanisms behind the increased Ks at 6 h are not clear. These results support a role for IGF-I in the posthatching muscle development of chicks.

(*Key words*: insulin-like growth factor-I, subcutaneous injection, muscle protein synthesis, serum glucose)

2002 Poultry Science 81:1543–1547

INTRODUCTION

Insulin-like growth factor-I (IGF-I) plays a role in the postnatal growth of numerous mammalian species. In chickens, hypophysectomy results in a reduction in growth rate and plasma IGF-I concentration. Sex-linked dwarf chickens, which lack a functional growth hormone receptor, also have significantly reduced levels of plasma IGF-I (Huybrechts et al., 1985; Tanaka et al., 1996), suggesting that IGF-I also contributes to postnatal growth in avian species. However, the exact nature of that contribution has been unclear, as there are conflicting reports showing that circulating IGF-I concentrations are not correlated (Goddard et al., 1988), negatively correlated (Pym et al., 1991), or positively correlated (McGuiness & Cogburn, 1990) with growth rate in chickens.

It is evident from studies in young chickens that a strong relationship exists between plasma IGF-I and nutrition, because fasting results in a decrease in plasma IGF-I that can be recovered upon refeeding (Morishita et al., 1993; Kita et al., 1996,1997). The fractional protein synthesis rate (K*s*) in the breast muscle of 1- or 2-wk-old chicks is decreased by fasting and is significantly related to the concomitant decrease in hepatic IGF-I mRNA expression (Kita et al., 1998). Also, Tomas et al. (1998) have demonstrated that infusion of recombinant human (rh)IGF-I into approximately 600- to 700-g chickens can significantly improve weight gain and nitrogen retention via a mechanism involving a reduced rate of muscle protein breakdown.

To help clarify the role of IGF-I in the early posthatching development of avian species, we have examined whether a single s.c. injection of rhIGF-I can influence K*s* in the breast muscle of 7-d-old chicks at selected points up to 24 h after injection and have related this to changes in serum IGF-I, glucose, and nonprotein nitrogen (NPN). We have used Single Comb White Leghorn chicks (layers) for this study as whole-body protein synthesis tends to be higher in layers than in broilers (Muramatsu et al., 1987), suggesting that they may be more responsive to factors influencing protein synthesis.

Received for publication July 30, 2001.

Accepted for publication May 18, 2002.

[1]To whom correspondence should be addressed: Michael.conlon@hsn.csiro.au.

[2]Present address: CSIRO Health Sciences and Nutrition, Kintore Ave., Adelaide, SA 5000, Australia.

[3]Hattori Yokei Ltd., Showa-ku, Nagoya, Japan.

Abbreviation Key: IGF = insulin-like growth factor; rh = recombinant human; K*s* = fractional protein synthesis rate; NPN= non-protein nitrogen.

MATERIALS AND METHODS

Experiment 1

Male Single Comb White Leghorn chicks were obtained on the day of hatching from Hattori Yokei Ltd.[3] Thereafter, chicks were maintained in steel cages in a temperature-controlled room (29 ± 1C) with continuous lighting and had free access to a commercial diet (Pre-Chick, Marubeni Siryou Ltd.[4]). At 7 d of age, chicks ranging in weight from 74 to 92 g were divided into eight separate treatment groups, containing 10 birds each. Chicks were distributed so that the average body weight per group was within a few grams of the overall average of 83 g. Each group of chicks was given a single s.c. injection of 200 μL of physiological saline, or 35 μg of rhIGF-I (GroPep Pty. Ltd.[5]) in physiological saline, into the dorsal region of the torso adjacent to the right wing.

After the injection, chicks were returned to their cages (with free access to food and water) until they were required for injection of ^{3}H-Phe (L-[2,6-3H]-Phe; 12 MBq/mol, Amersham Japan[6]) 2 min (four animals per group) or 10 min (six animals per group) prior to being killed. The ^{3}H-Phe was injected via a wing vein. Chicks were killed humanely by cervical dislocation at approximately 2 h 30 min, or 6, 12, or 24 h after the initial saline and IGF injections. A group of chicks injected with saline and a group injected with IGF-I were killed at each time point. Immediately after kill, blood was collected by heart puncture only from the chicks that had been injected with ^{3}H-Phe 10 min previously, whereas the breast muscle, pectoralis major, was excised from all chicks and immediately frozen in liquid nitrogen. Serum and muscle samples were stored at –20 C.

Measurement of the K*s* in breast muscle was by comparison of the specific activities of free and protein bound ^{3}H-Phe calculated from the values obtained from chicks killed 2 min and 10 min after ^{3}H-Phe injection, according to the method described by Garlick et al. (1980). This method allowed us to calculate K*s* in chicks killed at 10 min, for a maximum of six birds per treatment group.

Experiment 2

We examined the time course of serum IGF-I, glucose, and NPN changes after IGF-I injection into chicks of the same age and breeding (and identical experimental conditions) as for Experiment 1. Average body weight was 85 g (range 77 to 93 g). Chicks were killed, and serum was collected as previously described at 20 min, 1 h, 1 h 30 min, 2 h, 3 h, or 6 h after injection with saline or 35 μg rhIGF-I. There were six chicks per treatment group. All chicks in this second experiment were injected and killed on the same day. All other conditions and measurements, based on the method of Ballard et al. (1990), were as described by Kita et al. (1997). Glucose CII and NPN kits were obtained[7] for serum glucose and NPN assays, respectively.

Chick studies were carried out in accordance with the Nagoya University Policy on Animal Care and Use.

TABLE 1. Fractional synthesis rates (K*s*, %/d) of protein in the breast muscle of 7-d-old male Single Comb White Leghorn chicks at various times after injection of saline or 35 μg of recombinant human insulin-like growth factor-I (rhIGF-I) in saline (values represent the mean ± SEM; numbers in parentheses indicate n)[1]

Time after injection (h)	Saline	IGF-I
2.5	8.8 ± 0.8^{b} (5)	6.3 ± 0.6^{c} (6)
6	9.7 ± 1.1^{b} (4)	12.2 ± 1.5^{a} (4)
12	7.9 ± 0.3^{bc} (6)	7.7 ± 0.7^{bc} (5)
24	8.1 ± 0.6^{bc} (5)	8.9 ± 1.1^{b} (6)

[a-c]Values with no common superscript differ significantly ($P < 0.05$ except between IGF-I and saline treatments at 6 h where $P = 0.07$).

[1]K*s* was determined from the specific activities of free and protein bound. ^{3}H-Phe in breast tissue of chicks injected with ^{3}H-Phe before kill.

Statistical Analyses

Data from Experiment 1 were analyzed by two-way ANOVA to determine the effects of treatment and time, and the least significant difference test was used to compare between all means using the general linear models procedure. Data from Experiment 2 were analyzed by two-way ANOVA followed by a Tukey test. Significance was deemed to be $P < 0.05$ unless otherwise indicated.

RESULTS

Table 1 shows the results of Experiment 1 in which the K*s* in the breast muscles of chickens were measured at various times after s.c. injection with saline or 35 μg of rhIGF-I dissolved in saline. There was a significant interaction between treatment and time on protein synthesis, and the treatment effect was significantly higher 6 h after injection than at other times. Within 2 h 30 min of injection with IGF-I, breast muscle K*s* was significantly lower relative to the saline infused controls and was also lower than both treatment groups at 6 h. The K*s* in IGF-I-treated chicks at 6 h after injection was higher ($P = 0.07$) than for the saline-treated chicks at 6 h and was significantly higher than for IGF-I or saline-treated chicks at all other times. By 12 and 24 h, Ks had returned to within control levels in chicks injected with IGF-I.

Experiment 2 was carried out in the same way as Experiment 1, except that chicks were sacrificed more frequently after injections with saline or IGF-I to examine changes in serum IGF-I, glucose, and NPN leading up to the increased muscle K*s* observed at 6 h. Serum IGF-I concentrations (Figure 1) in samples from saline-infused chicks were at the lower limits of detection in the RIA (approximately 1 ng/mL) and are barely perceptible in the figure as a result. Within 20 min of injection with IGF-I, the serum concentration of IGF-I was 216 ± 59 ng/mL, which was significantly

[4]Marubeni Siryou Ltd., Chiyada-ku, Tokyo, Japan.
[5]GroPep Ltd., Thebarton, Adelaide, Australia.
[6]Amersham Japan, Shinjuku-ku, Tokyo, Japan.
[7]Wako Pure Chemical Industries Ltd., Chuo-ku, Osaka, Japan.

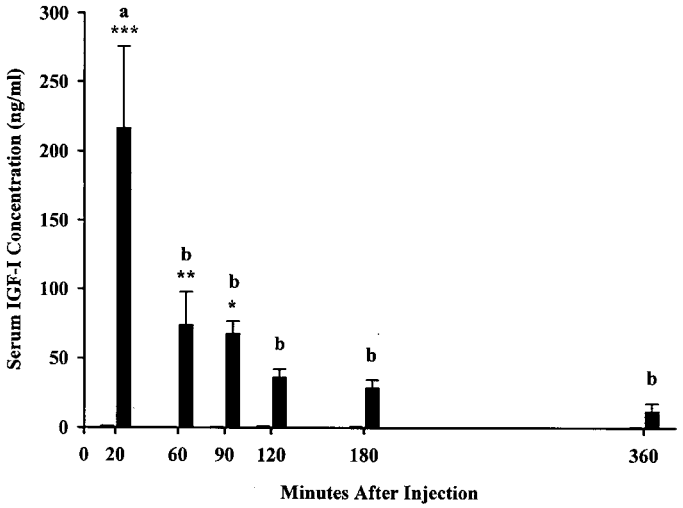

FIGURE 1. Concentrations of insulin-like growth factor-I (IGF-I) in serum collected from 7-d-old Single Comb White Leghorn chicks at various times after injection of saline (open bars; values are approximately 1 ng/mL and at the lower limits of detection) or 35 μg of recombinant human IGF-I in saline (filled bars). Bars represent the mean of each treatment group ± SEM (n = 6). ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ when compared to the respective saline control. [a,b]Comparison of IGF-I treatment means with time: bars not sharing a common letter are significantly different ($P < 0.05$). There were no significant differences between saline treatment means over time.

greater than for the saline control. The concentration decreased significantly thereafter but remained significantly higher than controls at 1 and 1.5 h after injection. The concentration at 6 h had declined to 12 ± 6 ng/mL.

Serum glucose concentrations are shown in Figure 2. IGF-I injection resulted in a significant decline in plasma glucose concentrations within 20 min compared to saline-infused controls. The decreased glucose concentration was maintained for at least 3 h after injection but returned to the same level as controls by 6 h. The concentrations of glucose in IGF-I-treated chicks did not differ significantly between the 20-min, 1-h, 1.5-, 2-, and 3-h time points, but all were significantly lower than the concentration at 6 h.

To gain a measure of serum amino acid concentrations, which may influence the response of muscle to IGF-I, we measured the serum concentration of NPN (Figure 3). Relative to saline controls, NPN was not altered within 20 min of IGF-I injection. By 1 h, however, concentrations relative to controls had decreased significantly and remained so even by 3 h. Concentrations appeared to have begun to return to those of saline-infused controls by 6 h but were nevertheless still significantly lower. When changes in NPN concentration after IGF-I injection were compared across time, only values at 1.5, 2, and 3 h were significantly lower than that at 20 min. Injection of saline resulted in a significant elevation of serum NPN levels relative to other time points at 1 h, and the concentration at 1.5 h was also significantly higher than that at 6 h.

DISCUSSION

The breast muscle of chickens grows more rapidly and has a higher rate of protein synthesis than other muscles during the first few weeks after hatching (Halvorsen and Jacobsen, 1970; Tesseraud et al., 1996). Also, the rate at which the breast muscle grows in proportion to body weight is greatest during the first 2 wk after hatching (Acar et al., 1993). Because IGF-I stimulates growth and protein synthesis of muscle cells in several species, we speculated that we would observe effects of IGF-I treatment on protein

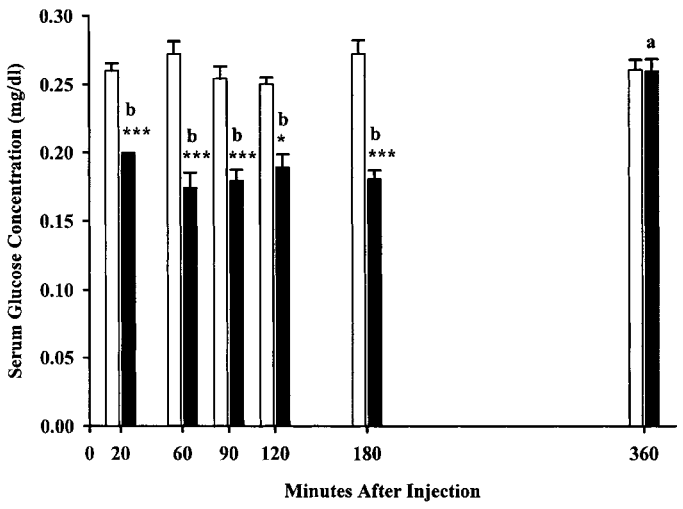

FIGURE 2. Concentrations of glucose in serum collected from 7-d-old Single Comb White Leghorn chicks at various times after injection of saline (open bars) or 35 μg of recombinant human insulin-like growth factor-I (IGF-I) in saline (filled bars). Bars represent the mean of each treatment group ± SEM (n = 6). ***$P < 0.001$, *$P < 0.05$ when compared to the respective saline control. [a,b] Comparison of IGF-I treatment means with time: bars not sharing a common letter are significantly different ($P < 0.05$). There were no significant differences between saline treatment means over time.

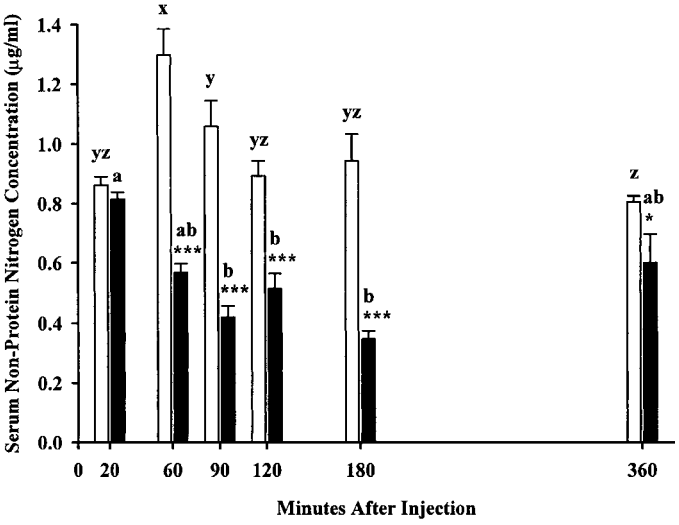

FIGURE 3. Concentrations of nonprotein nitrogen in serum collected from 7-d-old Single Comb White Leghorn chicks at various times after injection of saline (open bars) or 35 μg of recombinant human insulin-like growth factor-I in saline (filled bars). Bars represent the mean of each treatment group ± SEM (n = 6). ***$P < 0.001$, *$P < 0.05$ when compared to the respective saline control. [a,b]Comparison of IGF-I treatment means with time: bars not sharing a common letter are significantly different ($P < 0.05$). [x,y,z]Comparison of saline treatment means with time: bars not sharing a common letter are significantly different ($P < 0.05$).

synthesis in the breast muscle of 7-d-old chicks. Indeed, we have been able to demonstrate that a single injection of rhIGF-I could alter muscle protein synthesis rates in young chicks within at least 2 h 30 min and have related this finding to changes in the circulating concentrations of IGF-I, glucose, and NPN.

Attempts to stimulate the growth of chickens by treatment with IGF-I have been relatively unsuccessful (Huybrechts et al., 1992; Tixier-Boichard et al., 1992), adding to doubt about the role of IGF-I in the growth of the chicken. Nevertheless, the study by Tomas et al. (1998) has demonstrated that continuous infusion of IGF-I at 300 μg/kg body weight per day can improve weight gain in female broilers and also other strains of chickens with weights of between 600 and 700 g. Despite this result, Czerwinski et al. (1998) continuously infused recombinant chicken IGF-I into 3-wk-old (approximately 500 g), fed, meat-type, male broilers at 450 μg/kg body weight per day for 5 d but failed to stimulate weight gain or muscle (pectoralis and gastrocnemius) protein synthesis.

We administered a single 35-μg (approximately 410 μg/kg body weight) s.c. injection of rhIGF-I to 7-d-old layers and found that IGF-I can influence muscle protein synthesis with a decrease observed 2 h 30 min after injection and an increase approximately 6 h after injection.

Studies in vitro have shown IGF-I to stimulate protein synthesis and inhibit protein breakdown in L6 muscle cells (Ballard et al., 1986; Roeder et al., 1988). In rats, continuous infusion of IGF-I can increase carcass protein accretion and nitrogen retention (Tomas et al., 1993), and IGF-I can increase nitrogen retention in humans (Guler et al., 1987). IGF-I treatments can also reduce circulating glucose and amino acid concentrations (Jacob et al., 1989; Boulware et al., 1992; Elahi et al., 1993), and it is this reduction in the availability of glucose and amino acids after IGF-I injection that can counteract the ability of IGF-I to stimulate muscle protein synthesis in rats and humans (Jacob et al., 1989,1996; Mauras et al., 1992).

In the present study, injection of the growth factor into young chicks was associated with a lowering of blood glucose and NPN in the first few hours after injection, and it was within this period after injection, at 2 h 30 min, that we were also able to demonstrate an inhibition of muscle protein synthesis. Hence, it appeared as though low blood glucose or amino acids may contribute to an initial inhibition of K*s* after IGF-I injection in the chicken also. However, of more interest is the fact that by 6 h, K*s* was increased compared with rates in saline and IGF-I treatment groups at all other times.

In the study to examine changes in blood parameters, glucose was restored to normal but NPN was still significantly lower than saline controls at 6 h. The availability of glucose may therefore be critical in facilitating the stimulation of K*s* in the breast muscle of chicks. Insulin concentrations in blood would be expected to change along with those of glucose and may also play an important role in mediating effects of IGF-I on K*s*. The manner in which these and other factors influence the time-dependent changes in breast muscle protein synthesis in response to IGF-I is not clear and requires further investigation.

In our study, we treated chicks with the human form of IGF-I. A study by McMurtry et al. (1996) has shown that infused human IGF-I is cleared only slightly faster than chicken IGF-I from the blood of chickens aged between 7 and 8 wk. They showed that a considerable proportion of radiolabeled IGF-I infused into chicks is bound to a 150-kDa component of blood, likely to represent an IGF-binding protein complex, which is cleared at a much slower rate than free IGF-I. The human IGF-I bound to the 150-kDa component had a half-life of 453 min, and only traces of the radiolabeled IGF could be detected after 8 h. This finding is not inconsistent with our results because we were able to detect a gradual tapering off of IGF-I concentrations in blood over the 6 h following IGF-I injection.

Plasma IGF-I concentrations in 1-wk-old chickens are approximately four times lower than at 5 wk of age, when the posthatching peak in plasma concentration occurs (McMurtry et al., 1994). Circulating IGF-I binding capacity is also very low in the first few weeks after hatching but generally increases up to at least 12 wk of age (Schoen et al., 1992). Despite these increases during the posthatching period, the fractional synthesis rate of muscle protein is in steady decline (Tesseraud et al., 1996). Thus, it would appear that when circulating IGF-I concentrations are low, muscle protein synthesis is high. This finding indicates that some factors other than, or in addition to, IGF-I may be controlling protein synthesis during the first few weeks posthatching.

Because we have demonstrated that IGF-I can influence muscle protein synthesis during this period, there are likely to be functional IGF receptors present in the breast muscle. Indeed, IGF receptors can be found in chicken muscle cells as early as the embryonic stage (Trouten-Radford et al., 1991), and Matsumura et al. (1996) have isolated and sequenced a chicken IGF-I receptor cDNA and shown mRNA for the receptor to be expressed during the posthatching period. Of interest, however, was the fact that mRNA expression levels for the receptor in muscle and liver were very low relative to expression in many other tissues. This result is supported by the findings of McMurtry et al. (1996) that the incorporation of infused radiolabelled IGF-I into muscle tissue of young chickens is very low in comparison to that in other tissues, as this also suggests a low number of IGF receptors. These data would suggest that IGF-I-stimulated changes in muscle protein synthesis observed in our study were initially being mediated through a low population of the IGF-I receptor or were being mediated by a different pathway.

Our study indicates that a single injection of IGF-I can influence muscle protein synthesis in young chicks up to at least 6 h later, but the mechanisms underlying the effect remain to be elucidated.

ACKNOWLEDGMENTS

The work by M. Conlon was carried out with financial support from a Japan Society for the Promotion of Science

Post-Doctoral Fellowship. We thank M. Aman Yaman and R. Pinontoan for their guidance in measuring protein synthesis.

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