Nutritional and Tissue Specificity of IGF-I and IGFBP-2 Gene Expression in Growing Chickens* - A Review -

K. Kita**, K. Nagao and J. Okumura[1]**

Graduate School of Bioagricultural Sciences. Nagoya University. Nagoya 464-8601. Japan

ABSTRACT : Nutritional regulation of gene expression associated with growth and feeding behavior in avian species can become an important technique to improve poultry production according to the supply of nutrients in the diet. Insulin-like growth factor-I (IGF-I) found in chickens has been characterized to be a 70 amino acid polypeptide and plays an important role in growth and metabolism. Although it is been well known that IGF-I is highly associated with embryonic development and post-hatching growth, changes in the distribution of IGF-I gene expression throughout early- to late-embryogenesis have not been studied so far. We revealed that the developmental pattern of IGF-I gene expression during embryogenesis differed among various tissues. No bands of IGF-I mRNA were detected in embryonic liver at 7 days of incubation, and thereafter the amount of hepatic IGF-I mRNA was increased from 14 to 20 days of incubation. In eyes, a peak in IGF-I mRNA levels occurred at mid-embryogenesis, but by contrast, IGF-I mRNA was barely detectable in the heart throughout all incubation periods. In the muscle, no significant difference in IGF-I gene expression was observed during different stages of embryogenesis. After hatching, hepatic IGF-I gene expression as well as plasma IGF-I concentration increases rapidly with age, reaches a peak before sexual maturity, and then declines. The IGF-I gene expression is very sensitive to changes in nutritional conditions. Food-restriction and fasting decreased hepatic IGF-I gene expression and refeeding restored IGF-I gene expression to the level of fed chickens. Dietary protein is also a very strong factor in changing hepatic IGF-I gene expression. Refeeding with dietary protein alone successfully restored hepatic IGF-I gene expression of fasted chickens to the level of fed controls. In most circumstances, IGF-I makes a complex with specific high-affinity IGF-binding proteins (IGFBPs). So far, four different IGFBPs have been identified in avian species and the major IGFBP in chicken plasma has been reported to be IGFBP-2. We studied the relationship between nutritional status and IGFBP-2 gene expression in various tissues of young chickens. In the liver of fed chickens, almost no IGFBP-2 mRNA was detected. However, fasting markedly increased hepatic IGFBP-2 gene expression, and the level was reduced after refeeding. In the gizzard of well-fed young chickens, IGFBP-2 gene expression was detected and fasting significantly elevated gizzard IGFBP-2 mRNA levels to about double that of fed controls. After refeeding, gizzard IGFBP-2 gene expression decreased similar to hepatic IGFBP-2 gene expression. In the brain, IGFBP-2 mRNA was observed in fed chickens and had significantly decreased by fasting. In the kidney, IGFBP-2 gene expression was observed but not influenced by fasting and refeeding. Recently, we have demonstrated in vivo that gizzard and hepatic IGFBP-2 gene expression in fasted chickens was rapidly reduced by intravenous administration of insulin, as indicated that in young chickens the reduction in gizzard and hepatic IGFBP-2 gene expression in vivo stimulated by malnutrition may be, in part, regulated by means of the increase in plasma insulin concentration via an insulin-response element. The influence of dietary protein source (isolated soybean protein vs. casein) and the supplementation of essential amino acids on gizzard IGFBP-2 gene expression was examined. In both soybean protein and casein diet groups, the deficiency of essential amino acids stimulated chickens to increase gizzard IGFBP-2 gene expression. Although amino acid supplementation of a soybean protein diet significantly decreased gizzard IGFBP-2 mRNA levels, a similar reduction was not observed in chickens fed a casein diet supplemented with amino acids. This overview of nutritional regulation of IGF-I and IGFBP-2 gene expression in young chickens would serve for the establishment of the supply of nutrients to diets to improve poultry production. *(Asian-Aust. J. Anim. Sci. 2005. Vol 18, No. 5 : 747-754)*

Key words: IGF-I, IGFBP-2, Gene Expression, Nutrition, Tissue Specificity, Chickens

INTRODUCTION

It has been well recognized that growth hormone (GH)

** Corresponding Author: K. Kita. Laboratory of Animal Feeds and Production, Graduate School of Bioagricultural Sciences, University Farm, Nagoya University, Togo, Aichi 470-0151, Japan. Tel & Fax: +81-561-37-0203, E-mail: kitak@agr.nagoya-u.ac.jp

[1] Nagoya Bunri University, Inazawa 492-8520, Japan. Tel: +81-587-23-2400, Fax: +81-587-21-2844, E-mail: jokumura@nagoya-bunri.ac.jp

is one of anterior pituitary hormones and that GH release from pituitary gland is positively regulated by GH-releasing hormone (GHRH) and negatively by somatostatin from the hypothalamus. Recently novel peptidyl hormone 'ghrelin' that has the potency to stimulate GH release from the anterior pituitary was discovered (Figure 1). In rats and humans, ghrelin is a 28-amino acid acylated peptide and mainly produced in the stomach (Kojima et al., 1999). In avian species, chicken ghrelin was also purified and its cDNA was cloned. Chicken ghrelin was composed of 26 amino acids and possessed 54% sequence identity with human ghrelin. The potency of chicken ghrelin to increase plasma GH levels was similar to that of rat or human ghrelin (Kaiya et al., 2002). The main activity of GH in both avian and mammalian species is to stimulate growth
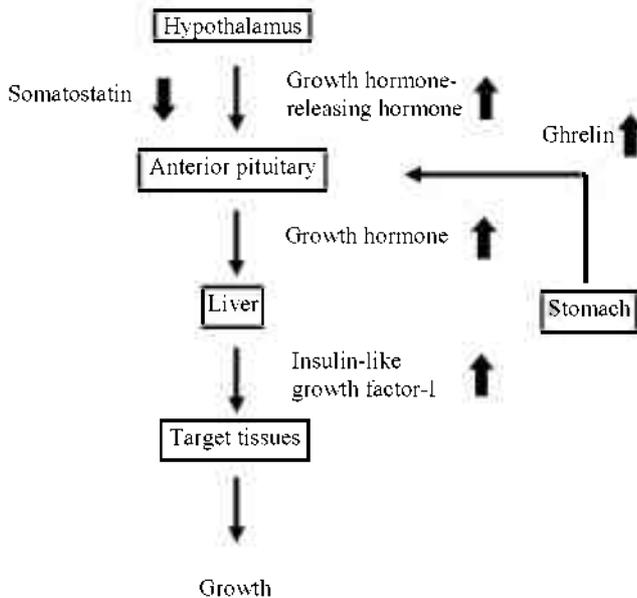
Hypothalamus

Somatostatin

Growth hormone-releasing hormone

Ghrelin

Anterior pituitary

Growth hormone

Liver

Stomach

Insulin-like growth factor-I

Target tissues

Growth

Figure 1. Schema of GHRH-GH-IGF-I axis.

rate of animals after their birth. The activity of GH is caused by its binding to a specific site of GH receptor followed by the alteration of conformation, so that the intracellular domains of GH receptor associate with a tyrosine kinase of the Janus family (JAK2). The signal transduction commenced from the binding of GH to its receptor can activate a specific gene coding IGF-I in a nuclear (Xu et al., 1995). The IGF-I released into the circulation binds to its specific receptor called by IGF type-1 receptor and finally stimulates cell proliferation. IGF-I found in chickens has been characterized and shown to be 70 amino acid polypeptide (Dawe et al., 1988, Ballard et al., 1990). Some findings pointing to an important role of IGF-I in the control of growth and metabolism in chickens, as in the case of mammals have been reported. For example, plasma IGF-I concentration was highly correlated with body weight gain caused by changes in nutritional conditions in young chickens (Kita et al., 1996b). The cDNA sequence of chicken IGF-I was cloned and characterized by Kajimoto and Rotwein (1989) and by Fawcett and Bulfield (1990). The structure of chicken IGF-I gene has also been investigated by Kajimoto and Rotwein (1991).

In most circumstances, IGF-I makes a complex with specific high-affinity IGF-binding proteins (IGFBPs). So far, six different IGFBPs have been found in mammals and their genes have also been cloned and identified (Shimasaki and Ling, 1991). IGFBPs are thought to prolong the half-life of circulating IGFs (Ketelslegers et al., 1996) and also act as modulators of IGF activity (Elgin et al., 1987; Rutanen et al., 1988). In the chicken, the major IGFBP in the plasma has been reported to be a 30 kDa protein corresponding to the bovine IGFBP-2 standard. Thus the predominant IGFBP

in chicken plasma differs from that in human plasma (Armstrong et al., 1989; Francis et al., 1990; Schoen et al., 1992; Upton et al., 1992; Morishita et al., 1993). Using the labeled chicken IGF-I as probe, a 30 kDa band in plasma samples from well-fed chickens was not detected. However, in plasma from chickens given restricted food intake or a low protein diet an intense band was observed at 30 kDa. The absence of the 30 kDa IGFBP in plasma of well-fed chickens indicated that chicken IGFBP-2 protein was produced when nutritional status was inadequate (Morishita et al., 1993; Kita et al., 1996b). Chicken IGFBP-2 cDNA and gene were cloned and the tissue distribution of IGFBP-2 mRNA in chicken embryos was examined (Schoen et al., 1995). However, available information about the relationship between nutrition and IGFBP-2 gene expression in young chickens has not been reported so far. Straus and Takemoto (1990) found in rats that decreasing dietary protein levels increased IGFBP-2 gene expression in the liver, and if this occur in young chickens, it may be an important mechanism for the regulation of IGFBP-2 levels in avian species.

As stated above, it seemed that in avian species as well as mammalian species changes in plasma levels of both IGF-I and IGFBP-2 would be regulated by alteration of transcriptional changes in both genes under various nutritional conditions. Therefore, in the present review, we summarized the nutritional regulation of gene expression of both IGF-I and IGFBP-2 in various tissues of young chickens.

TISSUE SPECIFICITY OF IGF-I GENE EXPRESSION

The *in vivo* studies of IGFs (IGF-I and IGF-II), which are structurally homologous to proinsulin, have demonstrated that IGFs bind to two specific cell surface receptors called IGF type 1 and 2 receptors (reviewed by Roth, 1988). IGF-I can bind IGF type 1 receptor with 15- to 20-fold higher than IGF-II (Germain-Lee et al., 1992). Studies using knock-out mice carrying null mutation of genes coding IGF-I and IGF type 1 receptor revealed the importance of both genes for embryonic development and postnatal growth (Baker, et al., 1993, Liu et al., 1993). During postnatal growth in rats, the expression of IGF-I gene was widely distributed in various tissues such as brain, lung, heart, stomach, diaphragm, kidney and testes and seemed to be the highest in the liver (Bornfeldt et al., 1989; Lowe et al., 1989). In avian species as well as mammalian species, IGF-I mRNA was also detected in extrahepatic tissues such as spleen, lung, brain, kidney, heart, intestine, thymus and muscle of growing chickens, and the most abundant expression of IGF-I mRNA was observed in the liver (Tanaka et al., 1996). Moreover, the direct evidence for the production of IGF-I in response to growth hormone has been found by using a chicken hepatocyte culture
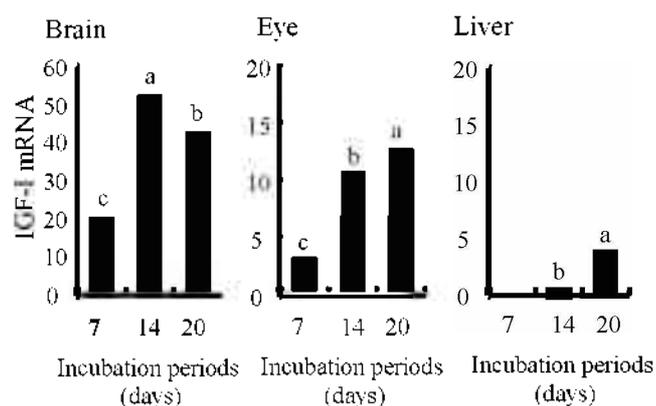
Figure 2. The IGF-I gene expression in the brain, eye and liver of chicken embryos. The number of tissues in each treatment was fifteen. Means not sharing with a common letter are significantly different at $P<0.05$ (a, b, c).

system (O'Neill et al., 1990; Houston and O'Neill, 1991), and it has been generally accepted that the liver is the major site of IGF-I production during post-hatch growing stages of chickens.

During embryogenesis of chickens, gene expression of IGF-I is distributed widely in various tissues as well as growing chickens. Serrano et al. (1990) reported that IGF-I mRNA transcripts in the pancreas and brain could be detectable by using RT-PCR while the levels in the liver were barely detectable in mid- and late embryogenesis (on days 12-18). Kikuchi et al. (1991) reported that on days 17 and 20 of incubation IGF-I mRNA was also detected in eyes, skeletal muscle and brain, but not found in the liver or heart until after hatching. Both researchers did not investigate gene expression of IGF-I throughout early-to late-embryogenesis, and therefore we studied the tissue distribution of IGF-I mRNA in various tissues at different stages of embryogenesis (Kita et al., 2000). In this report, IGF-I mRNA in eyes, heart, liver and breast muscle removed from chicken embryos at 7, 14 and 20 days of incubation was measured by using ribonuclease protection assay. As shown in Figure 2, it was revealed that extra-hepatic tissues produced IGF-I mRNA throughout embryogenesis and that the developmental pattern of IGF-I mRNA expression differed among the tissues examined. No bands of IGF-I mRNA were detected in the embryonic liver at 7 days of incubation, and thereafter the amount of hepatic IGF-I mRNA was quantified and increased from 14 to 20 days of incubation. This result was well supported by the previous findings reported by Serrano et al. (1990) using RT-PCR. In contrast to the liver, a protected IGF-I mRNA fragment was easily detected in eyes. In eyes, a peak in IGF-I mRNA levels occurred at mid-embryogenesis, but by contrast, IGF-I mRNA was barely detectable in the heart throughout all incubation periods. These results are consistent with previous reports by Kikuchi et al. (1991). In the muscle, no significant difference in IGF-I gene

expression was observed during different stages of embryogenesis. These results conclude that IGF-I gene expression in chicken embryos depends on the different stages of embryogenesis and extrahepatic tissues would play an important role for embryo growth.

NUTRITIONAL SPECIFICITY OF IGF-I GENE EXPRESSION

The impact of nutrients on gene expression has become an area of considerable interest as the number of genes coding key regulatory proteins in metabolic pathways were studied in detail. Especially, in mammalian species the regulation of transcription of the gene coding for phosphoenolpyruvate carboxykinase (PEPCK), a key enzyme in hepatic and renal gluconeogenesis, has been well investigated (Gurney et al., 1994). On the other hand, in avian species the analysis of physiological and molecular mechanisms by which diets and hormones regulate the activity of hepatic malic enzyme has been studied by a research group of Goodridge et al. (1991, 1996).

After hatching of chickens, plasma concentration and hepatic gene expression of IGF-I increase rapidly with aging, reach a peak before sexual maturity, and then decline (Huybrechts et al., 1985; Johnson et al., 1990; McGuinness and Cogburn, 1990; Kikuchi et al., 1991, Kita et al., 1997a). Plasma IGF-I level are also responsive to nutrition, i. e. varying dietary proteins, varying dietary energy intakes, food restriction (Rosebrough et al., 1992a, b; Rosebrough and McMurtry, 1993; Kita et al., 1996b; Rosebrough et al., 1996). Compared to plasma IGF-I concentration, in the chicken, studies on the response of hepatic IGF-I gene expression to different nutritional conditions has been limited. Food-restriction (Kita et al., 1996b) and fasting (Kita et al., 1998b, 2002a) decreased hepatic IGF-I gene expression and refeeding recovered it to the level of fed chickens, as was in good agreement with the changes in plasma IGF-I levels (Morishita et al., 1993; Kita et al., 1997b; Leili et al., 1997). Although the recovery of plasma IGF-I concentration by refeeding needed almost 48 h, hepatic IGF-I gene expression was increased within 24 h after refeeding in fasted young chickens (Kita et al., 2002a). The alterations in dietary protein and amino acid levels are also very strong factors to change plasma IGF-I concentration and hepatic IGF-I gene expression. Plasma concentration of IGF-I increased with elevating dietary protein levels from deficiency to the requirement level (Kita et al., 1996b, Kita and Okumura, 1999), and above the level, it decreased significantly (Kita and Okumura, 1999). Refeeding with dietary protein alone successfully restored hepatic IGF-I gene expression of fasted chickens to the level of fed control as well as that of chickens refed the complete diet (Kita et al., 1998a). In rat primary hepatocyto culture system, IGF-I gene transcription was decreased in
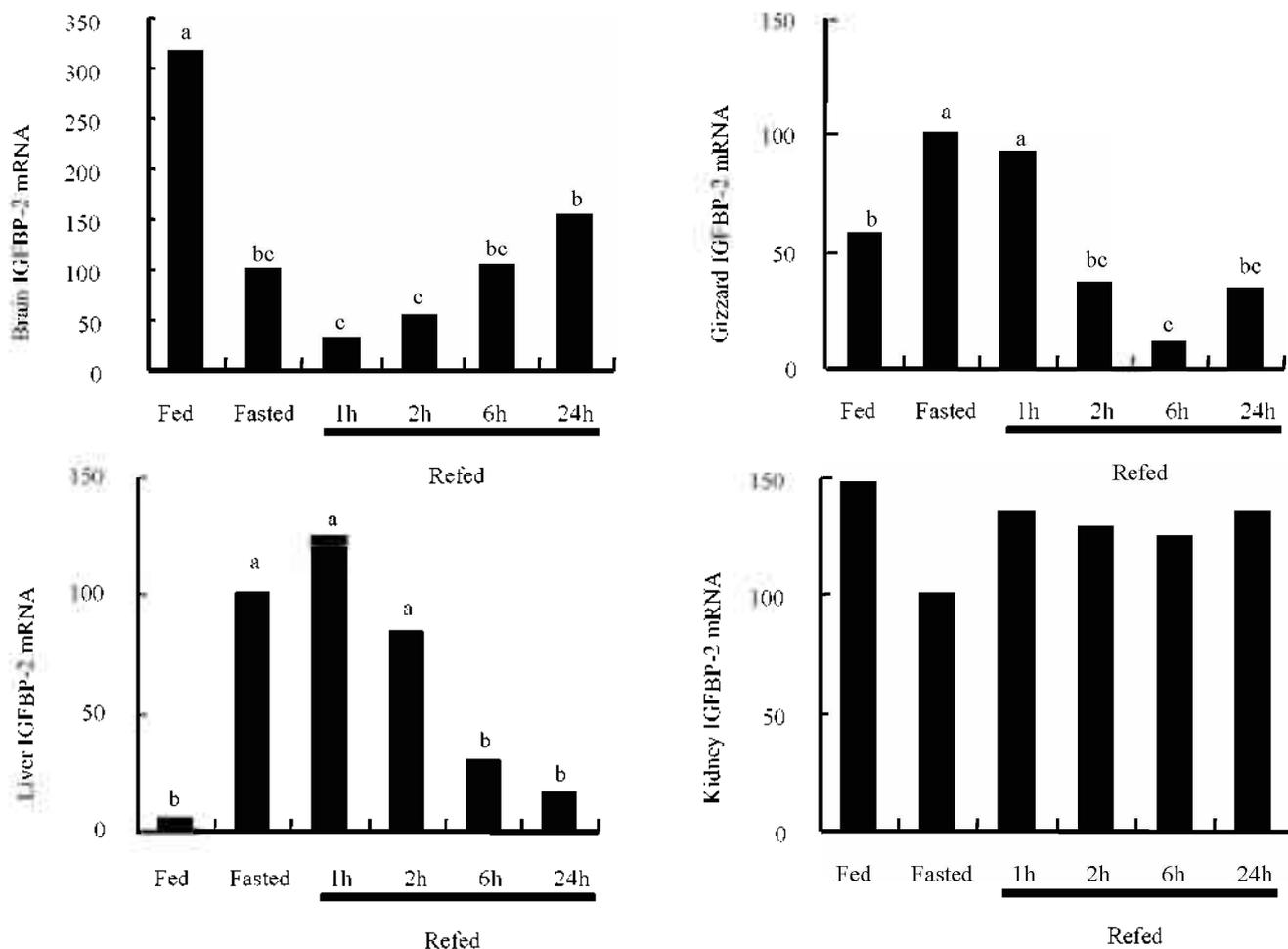
Figure 3. Time course changes in IGFBP-2 gene expression in the brain, gizzard, liver and kidney of fasted chickens after refeeding. Chickens were fasted for 2 d and then refed a commercial diet for 1, 2, 6 and 24 h. The number of birds in each treatment was five. Means not sharing a common letter are significantly different at $p<0.05$ (a, b, c).

response to reduced provision of amino acids in culture medium (Pao et al., 1993). Although there was virtually no findings on the influence of varying amino acid levels on hepatic IGF-1 gene expression in avian species, the influence of dietary amino acids on plasma IGF-I concentration has been investigated in the chicken. When young chickens were refed with protein-free diets containing either Gly alone or all essential amino acids after feeding with the protein-free diet alone, plasma IGF-I concentration was recovered to a level similar to that of fed chickens (Kita et al., 2002b). Deficient essential amino acids in diets sufficient with dietary protein requirement significantly reduced plasma IGF-I levels and amino acid supplement recovered it (Kita et al., 2002a). As it was known that changes in hepatic IGF-I gene expression was positively correlated to those in plasma IGF-I concentration (Kita et al., 1996b), hepatic IGF-I gene expression might, at least partially, regulate plasma IGF-I concentration in young chickens given varying amino acids levels. These issues should be elucidated in the near future.

NUTRITIONAL AND TISSUE SPECIFICITY OF IGFBP-2 GENE EXPRESSION

In avian species as well as mammalian species, it was revealed that IGF-I in the circulation makes a complex with IGFBPs, and cDNA sequences of several avian IGFBPs have been identified. In 1995, cDNA of IGFBP-2 was cloned by Schoen et al. (1995), and then IGFBP-5 cDNA was isolated by Allander et al. (1997). In 2003, two more IGFBP cDNAs (IGFBP-1 and IGFBP-4) were registerd in GenBank (IGFBP-1: GenBank accession no. CD214361 & CD214364, IGFBP-4: GenBank accession no. AY230206). However, cDNAs coding IGFBP-3 and IGFBP-6 were not identified so far.

In mammalian species, physiological and molecular analyses of six major IGFBPs have been well investigated. For example, the distribution of IGFBP-2 gene expression was precisely determined and it was reported that IGFBP-2 mRNA was abundant in brain, testes and ovary, moderately abundant in kidney, less abundant in liver and not detectable
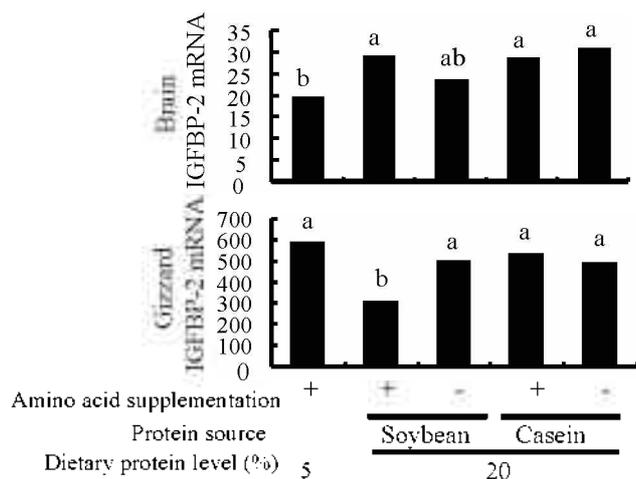
Figure 4. The IGFBP-2 mRNA in the brain and gizzard of young chickens fed a 20% soybean protein diet with (+) or without amino acids (-), 20% casein diet with (+) or without amino acids (-), or 5% soybean protein diet with amino acids. The number of birds in each treatment was five. Means not sharing a common letter are significantly different at $p<0.05$ (a, b, c).

in muscle and heart in adult rats (Margot et al., 1989). Although chicken IGFBP-2 cDNA was also cloned and IGFBP-2 mRNA was detected in various tissues of chicken embryos (Schoen et al., 1995), the distribution of IGFBP-2 gene expression has not been investigated in post-hatching chickens. Recently, therefore, we measured IGFBP-2 mRNA in various tissues of growing young chickens (Kita et al., 2002a). As shown in Figure 3, chicken IGFBP-2 mRNA was detected in the brain, gizzard, liver and kidney, but was barely detectable in the small intestine. In this study, it was also clarified that the abundant of IGFBP-2 mRNA in the brain, gizzard and liver was dependent on changes in nutritional conditions, and that in the kidney was independent.

We studied the relationship between nutritional status and IGFBP-2 gene expression in various tissues of chickens (Kita et al., 2002a). As shown in Figure 3, in the liver of fed chickens, almost no IGFBP-2 mRNA was detected. However, fasting markedly increased hepatic IGFBP-2 gene expression, and this level was retained even after 2 h of refeeding. After 6 h of refeeding, little IGFBP-2 mRNA could be detected in the liver. The response of hepatic IGFBP-2 gene expression to fasting and refeeding suggested two contrary functions of IGFBP-2 in plasma. Recently Hoeflich et al. (1999) made transgenic mice carrying mouse IGFBP-2 gene and revealed that overexpression of IGFBP-2 regulated postnatal growth negatively, potentially by reducing the bioavailability of IGF-I. Therefore, the first function of IGFBP-2 in plasma is the inhibitory activity, preventing IGF-I from associating with cell surface receptors and inhibiting IGF-I activity. Secondly, IGFBP-2 may act as stable reservoir of circulating free IGF-I, which is readily degraded by

protease especially under malnutritional conditions. Furthermore, McMurtry et al. (1996) showed that IGF-I associated with IGFBPs had a longer half-life compared to free IGF-I. Therefore, the rapid increase in tissue IGFBP-2 gene expression by fasting would serve for providing a large amount of circulating IGFBP-2 to prevent the proteolysis of IGF-I by making IGF-IGFBP complex in plasma.

In the gizzard of well-fed young chickens, IGFBP-2 gene expression was detected and fasting significantly elevated gizzard IGFBP-2 mRNA levels to about double that of fed controls (Figure 3). After 1 h of refeeding, gizzard IGFBP-2 gene expression remained at a level similar to fasted chickens, but thereafter the level of IGFBP-2 mRNA decreased to that of fed controls. Although gizzard is recognized as one of gastrointestinal organs specific in avian species, the relation of gizzard IGFBP-2 gene expression to changes in nutritional conditions has not been clarified so far. Therefore, we investigated the influence of fasting and refeeding on gizzard IGFBP-2 gene expression and revealed that the response in gizzard IGFBP-2 gene expression showed similar trend to that observed in the liver. This suggests that the regulatory mechanisms of plasma IGFBP-2 concentration may be attributed to the changes in IGFBP-2 gene expression in the liver and gizzard.

In the brain, IGFBP-2 mRNA was observed in fed chicks and had significantly decreased by 2 days of fasting (Figure 3). Decreased IGFBP-2 gene expression in the brain was not recovered to the level of well-fed chickens after refeeding for 24 h. On the other hand, in the kidney, IGFBP-2 gene expression was observed but not influenced by fasting and refeeding. Several years ago, Schoen et al. (1995) have characterized a genomic DNA for chicken IGFBP-2 and revealed that it contained insulin response element in the 5' upstream region. Similar insulin response elements have been identified in both human IGFBP-1 (Suwanickul et al., 1993) and rat IGFBP-3 genes (Villafuerte et al., 1997), whose expression is negatively regulated by insulin. Recently, we have demonstrated in vivo that gizzard and hepatic IGFBP-2 gene expression increased by 2 day-fasting was rapidly reduced by intravenous administration of bovine insulin in young chickens (Nagao et al., 2001). These results indicated that in young chickens the reduction in gizzard and hepatic IGFBP-2 gene expression in vivo stimulated by malnutrition might be, in part, regulated by means of the increase in plasma insulin concentration via an insulin-response element. Moreover, as it was reported that insulin repression of IGFBP-1 gene expression was dependent on the mammalian target of rapamycin (mTOR), but independent of ribosomal S6 kinase activity (Patel et al., 2002), similar mechanism would exist in the regulatory

process of IGFBP-2 gene expression.

The influence of dietary protein source (isolated soybean protein vs. casein; crude protein (CP) 20%) and the supplementation of essential amino acids on IGFBP-2 gene expression in the brain and gizzard of young chickens was examined (Kita et al., 2002a). In this study, the influence of feeding a low protein diet (CP 5%) on tissue IGFBP-2 gene expression was also investigated. As shown in Figure 4, feeding the low protein diet significantly decreased the level of brain IGFBP-2 mRNA and increased gizzard IGFBP-2 level, which indicated that the influence of dietary protein deficiency on tissue IGFBP-2 gene expression seemed to be similar to the case of fasting. The significant interaction between protein source and amino acid supplementation was observed in gizzard IGFBP-2 mRNA level. In both soybean protein and casein diet groups, the deficiency of essential amino acids stimulated to increase gizzard IGFBP-2 gene expression to the level of low protein diet group. Although the amino acid supplementation into soybean protein diet significantly decreased gizzard IGFBP-2 mRNA level, similar reduction was not observed in chickens fed a casein diet supplemented with amino acids. It was reported that serum amino acid concentrations were considerably different in rats given either dietary casein or isolated soybean protein (Horigome and Cho, 1992). Moreover, a few evidences pointed out directly that several amino acids had the potency to regulate the expression of hepatic IGFBP-1 gene (Pao et al., 1993; Jousse et al., 1998; Takenaka et al., 2000a, 2000b). These findings suggested that different response in gizzard IGFBP-2 gene expression to different dietary protein source, casein and isolated soybean protein, might be resulted by the change in serum amino acid concentrations, and this issue should be elucidated in the future.

CONCLUSION

The impact of nutrients on gene expression has become an area of considerable interest as the number of genes coding of growth promoting and regulating proteins are studied in detail. In mammalian species, recently, the role for promoter region to regulate IGFBP-1 gene according to nutritional manipulation has been investigated precisely and detailed knowledge has been accumulating. Compared to mammalian species, the information of regulatory mechanism of IGFBPs in avian species has been considerably limited. As our research indicated that varying dietary nutrients have the potency to improve poultry production through nutritional manipulation of several genes coding IGF-I and IGFBPs. We expect that the advanced works to reveal nutritional regulation of avian growth factors and their binding proteins will be conducted in the near future.

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