Recent Advances in the Relationship between Endocrine Status and Nutrition in Chickens[a]
- Review -

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ABSTRACT : A large number of investigations have shown that changes in nutritional condition affect endocrine status in avian species. Herein, recent findings including novel peptides discovered by the development of the techniques in the field of molecular biology have been reviewed. The insulin-like growth factors (IGF-I and IGF-II) found in chickens have been characterized and shown to be 70 and 66 amino acid polypeptides, respectively. Plasma IGF-I level is very responsive to nutrition, i.e. varying dietary proteins and energy intakes, and food restriction. Plasma IGF-II concentration is altered by nutritional deprivation to a much smaller extent than plasma IGF-I concentration. Almost all of the serum and tissue IGFs are found in a complex composed of IGF and IGF-binding protein (IGFBP). In the chicken plasma, the major IGFBP differs from that in mammalian plasma. The proglucagon mRNA encodes glucagon and two glucagon-like peptides (GLP-1 and GLP-2). The intracerebroventricular administration of GLP-1 strongly decreased food intake of chicks, and it was indicated that the inhibition of food intake by GLP-1 was associated with neuropeptide Y, which is one of the neurotransmitters reported to enhance food intake. (*Asian-Aus. J. Anim. Sci. 1999. Vol. 12, No. 7 : 1135-1141*)

Key Words : Nutrition, Chickens, Insulin-Like Growth Factors, Glucagon-Like Peptides, Thyroid Hormones, Pancreatic Hormones

INTRODUCTION

The influence of changes in nutritional condition on endocrine status has been the subject of intense investigation in the field of poultry production. The past decades have brought startling advances in clarifying the relationship between nutrition and endocrine in the poultry. A large number of investigations has shown that in avian species as well as mammalian species some hormones, i.e. growth hormone (GH), insulin, glucagon, thyroid hormones, corticosterone, can play an important role for modulating metabolic status and promoting cell proliferation and differentiation from embryonic stage to post-hatch growing period. Recently, especially in the last decade, the development of the techniques in the field of molecular biology and biotechnology led to the discovery of novel peptides associated with the nutrition of the poultry. Interestingly, these peptides have homologous amino acid and cDNA sequences similar to those of well-known hormones. For example, insulin-like growth factor-I and -II (IGF-I and IGF-II), which have been purified from chicken serum, are highly homologous in the amino acid and cDNA sequences to those of proinsulin. Glucagon-like peptide-1 and -2 (GLP-1 and GLP-2) have been characterized in cDNA sequence of proglucagon. Recent studies have shown that these newly discovered peptides are also closely related to the nutritional status of poultry. In this paper, therefore, we have focused on several hormones and peptides involving IGFs and GLPs, and reviewed recent work examining the relationship between change in nutritional status and these hormones in avian species.

INSULIN

In higher vertebrates, the relatively constant level of blood glucose concentration is maintained by several hormones. Insulin and glucagon, which are secreted from the pancreas, are the principal hormones to control plasma glucose concentration. After the first extraction of insulin (Banting and Best, 1922), biological activities of crude fowl pancreatic extract containing insulin were assayed. The first purification of fowl insulin was achieved by Mirsky et al. (1963). Thereafter, a large number of studies have been conducted to clarify the characteristic of insulin itself and its physiological aspects in nutrition. Fasting is one of the severest nutritional conditions for mammalian and avian species. In both species, fasting decreases the level of blood glucose (Harvey et al., 1978; Langslow et al., 1970; Rosebrough et al., 1984), and glucose concentration increases within 30 min of refeeding (Krestel-Rickert et al., 1986). In these nutritional conditions, changes in plasma insulin

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concentration are correlated to those of glucose levels. Simon and Rosselin (1978) reported that orally administrated amino acid mixture also stimulated insulin release in the chicken.

It has been well known that insulin is a multipotent hormone in that it has wide influence directly and indirectly on fat and protein metabolism. For example, in skeletal and heart muscles, insulin is potent to increase free fatty acid synthesis (Gomez-Capilla et al., 1980). In an *in vitro* study, hepatocytes incubated in serum-free medium containing chicken insulin had greater rates of triglyceride synthesis than insulin-unexposed cells (Laurin and Cartwright, 1993). Compared to fat metabolism, insulin affects protein metabolism to a smaller extent. Recent studies indicate that the main pathway of anabolic effects of insulin and IGF-I to stimulate protein metabolism is via IFG type-1 receptor and the lower influence on protein metabolism may result from lower affinity of insulin to IGF-I receptor than to insulin receptor (Rechler and Nissley, 1985).

GLUCAGON

In contrast to the anabolic reaction of insulin for carbohydrates, proteins and fats, glucagon can be thought of as an indirect antagonist of insulin, which leads to hypoglycemic conditions. Pollock and Kimmel (1975) isolated chicken glucagon during the preparation of insulin and showed that it contains one more serine residue than the porcine hormone and one less aspartic acid residue. The complete amino acid and cDNA sequences of chicken glucagon were determined by Solomon et al. (1987) and by Hasegawa et al. (1990), respectively.

A large number of studies to investigate the influence of glucagon on metabolism have been conducted. The injection of mammalian pancreatic glucagon increased the plasma glucose and free fatty acid concentrations (Ketterer et al., 1967; Freeman, 1982). In their *in vitro* study, Watkins et al. (1997) demonstrated that acute inhibition of fatty acid synthesis by glucagon is regulated by the change in cAMP. Some recent work on the influence of glucagon has focused on the lipolysis stimulated by this hormone in adipocytes. Although it has been known that both glucagon and GH stimulated lipolysis in the chicken, Harden and Oscar (1993) showed that glucagon does not act with triiodothyronine (T_3) and GH synergistically to increase lipolysis from broiler adipocytes. Oscar (1996) measured the affinity and concentration of glucagon receptor by using a radio-receptor assay and showed that decreased glucagon binding was closely associated with reduced lipolysis, implicating down-regulation of cell-surface glucagon receptors in the mechanism whereby glucagon induces desensitization of its ability to acutely stimulate lipolysis in broiler adipocytes. These findings suggests that glucagon may act on lipid widely and that its effect is independent from GH and thyroid hormones.

THYROID HORMONES

It has been well recognized that the thyroid hormones play a major role in growth, development and metabolism of mammalian and avian species (King and May, 1984). In avian species, triiodothyronine (T_3), but not thyroxine (T_4), is essentially active in stimulating metabolic or hormonal responses in chickens, and the relationship between the thyroid function and nutritional status has been widely studied. Consumption of a low protein diet often causes elevation in circulating levels of thyroid hormones and occurrs independently of the sources of dietary carbohydrate and fat replacing protein to formulate the low protein diet (Carew and Alster, 1997). Recently Carew et al. (1997) evaluated the effect of individual essential amino acid deficiencies on plasma thyroid hormone concentrations. In this report, they showed that plasma T_3 levels in the group deficient in arginine, lysine, isoleucine or methionine were higher than in their respective pair-fed controls, and concluded that changes in circulating levels of T_3 in a protein deficiency may be a consequence of particular amino acid deficits. Dietary excesses of isolecine and valine increased plasma T_3; levels were statistically higher than control levels (Carew et al., 1998).

Several studies revealed a decrease in abdominal fat by T_3 administration (Tixier-Boichard et al., 1992). In an *in vitro* study, it has been demonstrated that T_3 decreased hepatic lipogenesis (Rosebrough et al., 1992a) and increased adipocyte lipolysis (Harden and Oscar, 1993). As Vasilatos-Younken and Scanes (1991) pointed out, there is evidence that T_3 function for fat metabolism is associated with GH action (Cabello and Wrutniak, 1989). When chickens were chronically given GH plus T_3 (Harden and Oscar, 1993), carcass fat content was greatly reduced (Cogburn et al., 1989). In an *in vitro* study, however, the effect of GH on adipocyte lipolysis was independent from that of T_3 (Harden and Oscar, 1993) it appeared that the interactive effect of T_3 and GH in decreasing carcass fat content may act during lipogenesis.

Malic enzyme, which is one of the set of lipogenic enzymes, is a cytoplasmic protein which catalyzes the oxidative decarboxylation of malate to pyruvate and CO_2. It has been well known that liver is the primary site for the de novo synthesis of fatty acids in birds (Goodridge and Ball, 1967; Goodridge, 1968). Goodridge et al. (1989) reviewed the nutritional and hormonal regulation of the gene for avian malic enzyme, in which T_3 is one of positive effectors

playing the major positive role in regulating hepatic malic enzyme. They used the chick embryo hepatocytes culture system and revealed that T_3 alone caused a significant increase in transcription of malic enzyme within 1 h, with a maximal increase of more than 10-fold compared to control (Back et al., 1986). Thereafter, Salati et al. (1991) reported that T_3-stimulated transcription of the malic enzyme gene did not require ongoing protein synthesis. To study the characterization of the regulatory mechanisms involved in the gene of chicken malic enzyme, fragments of genomic DNA spanning the structural and 5'-flanking regions of its gene were cloned by Hodnett et al. (1996). They revealed that when 5'-flanking region of chicken malic enzyme gene linked with chloramphenicol acetyltransferase reporter gene was transiently transfected into chick-embryo hepatocytes, 5800 bp of 5'-flanking DNA contains the T_3 response element. Recently, it was reported that the inhibition of malic enzyme gene transcription caused by medium-chain fatty acids may be mediated through cis-acting T_3 response elements and trans-acting T_3 receptors (Thurmond et al., 1998).

INSULIN-LIKE GROWTH FACTOR-I AND-II (IGF-I, IGF-II)

Growth hormone (GH), which is one of anterior pituitary hormones, has several major activities (figure 1). The main activity of GH in both avian and mammalian species is to stimulate growth rate of animals after their birth. Recent work revealed the mechanism of signal pathway from the release of GH from pituitary to the expression of animal growth. The activity of GH is brought about 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. The IGF-I released into the circulation binds to its specific receptor called by IGF type-1 receptor and finally stimulates cell proliferation.

The insulin-like growth factors (IGF-I and IGF-II) found in chickens have been characterized and shown to be 70 and 66 amino acid polypeptides, respectively (figures 2 and 3; Dawe et al., 1988, Ballard et al., 1990, Kallincos et al., 1990). Recently some findings pointing to an important role for IGF-I in the control of growth and metabolism in chickens, as with mammals, have been reported. After hatching, 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). Plasma IGF-I level is also responsive to nutrition, i.e. varying dietary proteins, varying dietary energy intakes, food restriction (Rosebrough et al., 1992a, b; Rosebrough and McMurtry, 1993, Rosebrough et al., 1996; Kita et al., 1996b). Plasma concentration of IGF-I increased with elevating dietary protein levels from deficiency to the requirement level (Kita et al., 1996b), and above the level, it decreased significantly (Kita et al., 1999). As shown in figure 4, food-restriction and fasting also decreased plasma IGF-I concentration and with refeeding recovered to the level in fed chickens (Kita et al., 1996b); this is in good agreement with other studies (Morishita et al., 1993; Kita et al., 1997b; Leili et al., 1997). In our *in vitro* study, we demonstrated that the lowered activity of food-deprived chicken serum for protein synthesis in chicken embryonic fibroblasts was associated with a reduction in IGF-I concentration in the serum (Kita et al., 1996b). These results suggested that the change in plasma IGF-I concentration under various nutritional conditions is closely associated with body weight change.

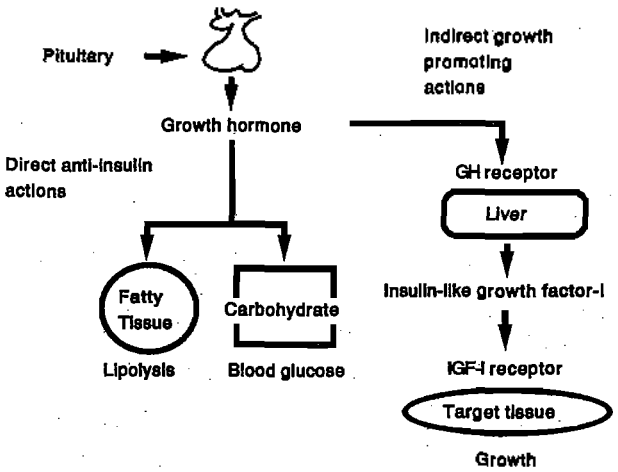

Figure 1. Schema of the actions of growth hormone

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). Since these studies, the probes to detect chicken IGF-I mRNA in total RNA samples extracted from various tissues have been avaliable, and the relationship between nutrition and chicken IGF-I gene expression was investigated. Feeding of a low protein diet reduced hepatic IGF-I gene expression following a decrease in plasma IGF-I concentration of young broiler chickens (Kita et al., 1996b). Food-deprivation also decreased hepatic IGF-I mRNA levels chickens at early stages of growth (Kita et al., 1997a).

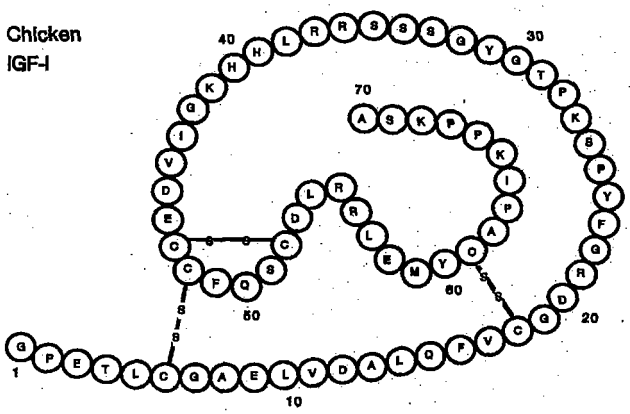

Figure 2. Amino acid sequence of chicken insulin-like growth factor-I (IGF-I) (Ballard et al., 1990)

Chicken
IGF-II

YGTAETLCGGELVDTLQFVC
GDRGFYFSRPVGRNNRRINR
GIVEECCFRSCDLALLETYC
AKSVKSE

Figure 3. Amino acid sequence of chicken insulin-like growth factor-II (IGF-II) (Darling and Brickell, 1996)

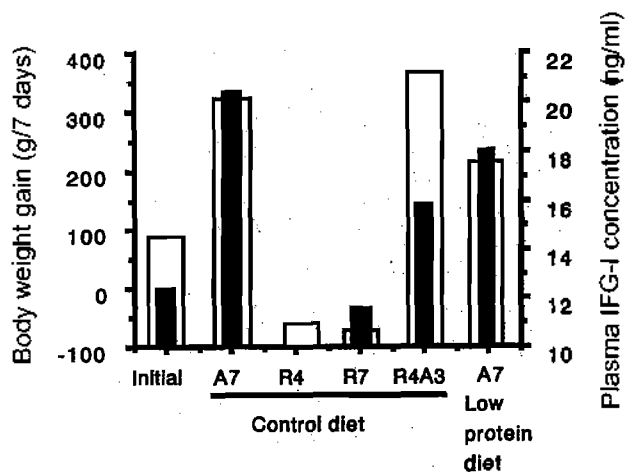

Figure 4. Body weight change (solid bar) and plasma IGF-I concentration (open bar) in meat-type chickens under various nutritional conditions. Crude protein contents in the control and low protein diets were 20% and 10%, respectively. Abbreviations: A, ad libitum; R, restricted feeding corresponding to the half of food intake ad libitum measured for 3 days before the commencement of the experiment (Kita et al., 1996b).

In contrast to the studies related to IGF-I, there is virtually no information on circulating IGF-II concentrations in avian species. Scanes et al. (1989) measured plasma concentration of IGF-II in young chickens in which they reported no correlation between IGF-II concentration and assessment of the functional role of IGF-II in growth and metabolism in chickens. Previously, we have examined the influence of nutrition on plasma IGF-II concentration in young meat-type chickens using radioimmunoassay with recombinant chicken IGF-II as standards (Kita et al., 1996b). In this study, there was no significant influence of nutrition on plasma IGF-II concentration, which is not in agreement with the results Scanes et al. (1997) who reported that plasma IGF-II concentration was lowered by nutritional restriction. It is concluded that plasma IGF-II concentration in the chicken is altered by nutritional deprivation, but to a much smaller extent than plasma IGF-I concentration.

Almost all of the serum and tissue IGFs are found in a complex composed of IGF and a specific protein which can bind to IGFs (figure 5). There are six IGF-binding proteins (IGFBPs) and some IGFBP-related peptides. 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 (Francis et al., 1990; Upton et al., 1992; Schoen et al., 1992; Morishita et al., 1993b). Using the labelled chicken IGF-I as probe, we did not observe a 30-kDa band in plasma samples from well-fed chickens. 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 indicates that this IGFBP is produced when nutritional status is inadequate (Morishita et al., 1993a; Kita et al., 1996b).

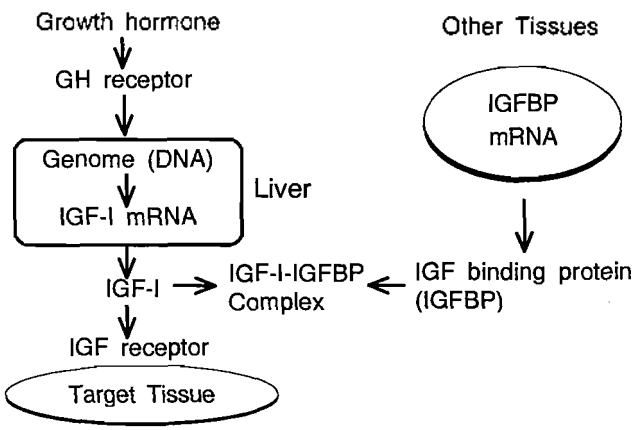

Figure 5. Schema of the relationship between IGF-I and IGFBP

Recently 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). So far, no information about the relationship between nutrition and IGFBP-2 gene expression has been published. Straus and Takemoto (1990) found that decreasing dietary protein levels increased IGFBP-2 gene expression in the young rat liver, and if this occur in chickens, it may be an important mechanism for the regulation of levels of the IGFBP-2 in chickens. This issue should be elucidated in the future.

GLUCAGON-LIKE PEPTIDE-1 AND-2 (GLP-1, GLP-2)

In mammalian species, the proglucagon gene is transcribed into a single identical mRNA in the pancreas, intestine and brain. The proglucagon mRNA encodes glucagon and two glucagon-like peptides (GLP-1 and GLP-2) (figure 6). The analysis of chicken pancreatic cDNA library to isolate chicken glucagon cDNA revealed that pancreatic proglucagon cDNA encodes glucagon and only one GLP-1 (Hasegawa et al., 1990). However, the isolation of intestinal proglucagon cDNA from chickens showed that the proglucagon gene also contains the sequence of GLP-2 (Irwin and Wong, 1995). The difference between pancreas and intestine was accounted for by different alternative mRNA splicing.

Chicken GLP-1	HSEFERHAEGTYTSD ITSYLEGQAAKEFIA WLVNGRG
Chicken GLP-2	HADGTFTSDINKILD DMAAKEFLKWLIN人 VTQ

Figure 6. The predicted amino acid sequences of chicken glucagon-like peptide (GLP)-1 (Hasegawa et al., 1990) and -2 (Irwin and Wong, 1995)

As represented in figure 7, the intracerebroventricular administration of GLP-1 strongly decreased food intake of chicks, similar to its effect in rats (Furuse et al., 1997b). In this report, chicken GLP-1 was similarly potent to inhibit food intake compared to mammalian GLP-1. Thereafter, it was indicated that the inhibition of food intake by intracerebroventricular administration of GLP-1 was associated with neuropeptide Y (NPY), which is one of the neurotransmitters reported to enhance food intake (Furuse et al., 1997a). Previously, Howes and Forbes (1987) reported that the suppression of food intake caused by the peripheral administration of glucagon was not observed when chickens were vagotomized at the level of the proventriculus. These results suggest that the family of glucagon and GLPs may react with the central and peripheral nervous system to regulate food intake of the chicken.

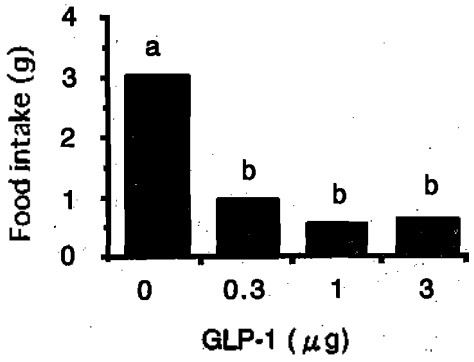

Figure 7. The influence of intracerebroventricular GLP-1 administration on food intake of chicks (Furuse et al., 1997)

CONCLUSION

As stated in the above sections, even in the field of poultry science, the biochemical, physiological and molecular biological aspects of several hormones have been widely and deeply investigated by many researchers, and a large amount of information on these hormones has been accumulated. As well as hormones reviewed in this paper, many other hormones potent to regulate nutritional metabolism have been discovered in avian species. Moreover, the development of new technology will give us the chance to discover new peptides and some of these newly discovered peptides may be associated with nutrition. We expect that the relationship between these new peptides and nutritional status will be revealed in the near future.

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