

Conference: Nutritional and Developmental Roles of Insulin-like Growth Factors between Species

Nutritional and Developmental Roles of Insulin-like Growth Factors in Poultry¹

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ABSTRACT Insulin-like growth factor-I and -II are important multifunctional polypeptides that interact with membrane-bound receptors as well as soluble binding proteins. The biological actions of these hormones are multifaceted and dependent to a large extent on binding protein interactions. Some unique differences in insulin-like growth factor physiology and biochemistry are evident between mammalian and avian species. These include amino acid compositional and significant receptor differences as well as binding protein status. The biological response to both growth factors is different in birds. A greater proportion of the insulin-like growth factors exists in plasma as free peptide compared with the situation in mammals. This review is a brief summary of our knowledge of insulin-like growth factor physiology in domestic fowl. *J. Nutr.* 128: 302S–305S, 1998.

KEY WORDS: • *chickens* • *turkeys* • *metabolism* • *hormone*

INTRODUCTION

This discussion will focus on the role of insulin-like growth factor-I and -II in development and intermediary metabolism in avian species, primarily the chicken. Results from recent studies indicate that unique interspecies differences exist with regards to growth factor biochemistry and physiology. This is best illustrated by the observations that differences exist between chickens and mammals in the amino acid composition of IGF-I and IGF-II (Ballard et al. 1990, Upton et al. 1995). More distinctive is the fact that although the cation-independent mannose 6-phosphate receptor is present in chicks, it does not bind IGF-II, suggesting that the actions of IGF-II are mediated by the type 1 receptor (Zhou et al. 1995). Also, a preliminary report suggested that the metabolic action of IGF-I in birds may be different from that in mammals (McMurtry et al. 1996a). A more detailed review of the role of the IGF in avian development and metabolism has been reported (McMurtry et al. 1997).

CHICKEN INSULIN-LIKE GROWTH FACTORS

The presence of IGF-I in birds was confirmed by the complete amino acid sequencing of IGF-I purified from chicken plasma, which established the presence of eight amino acid substitutions compared with mammalian IGF-I (Ballard et al. 1990). Only minor differences in biological properties between

mammalian and chicken IGF-I have been identified. However, differences in clearance rates from the circulation of chickens between human and chicken IGF-I and -II have been reported (McMurtry et al. 1996b). This most likely reflects differences in the interaction of the IGF with their binding proteins.

Characterization of serum purified chicken IGF-II by complete amino acid sequencing (Kallincos et al. 1990) indicated 13 amino acid differences compared with human IGF-II. In chicken IGF-II, six of the 13 differences occur in the C-domain sequence.

INSULIN-LIKE GROWTH FACTOR RECEPTORS

Classical type 1 IGF receptors in poultry have been described by a number of groups (see review, McMurtry et al. 1997). In contrast to the situation in mammals, there is no evidence for a second IGF receptor in chickens. Nucleotide sequencing determined that the chicken cation-independent mannose-6-phosphate receptor differed from its mammalian homologues in that it did not have residues equivalent to those in the mammalian receptor that are thought to be involved in binding IGF-II (Zhou et al. 1995). Recently, a high-molecular-weight IGF-II binding protein-like protein has been detected in turkey plasma (McMurtry et al. 1996c) and chick plasma (Kita et al. 1996, McMurtry et al. 1996b), which may function as a soluble IGF-II receptor.

The type 1 IGF receptor has been identified in the avian embryo as well as in tissues derived from embryos (DePablo et al. 1993). In birds after hatching, type 1 receptors have been quantified in cells derived from turkey muscle (Minshall et al. 1990), various tissues in the turkey (McFarland et al. 1992) and in chick hepatocytes (Duclos and Goddard 1990). Beyond these few reports, nothing is known with regard to IGF receptor activity in other highly metabolic tissues, such as fat and bone.

¹ Presented as part of the 62nd Annual Poultry Nutrition Conference "Nutritional and Developmental Roles of Insulin-like Growth Factors between Species" given at the Experimental Biology 97 meeting, April 6, 1997, New Orleans, LA. This conference was sponsored by the American Society for Nutritional Sciences and supported in part by Elanco Animal Health, A Division of Eli Lilly and Company, and Shaver Poultry Breeding Farms Limited. Guest editor for the symposium publication was Douglas C. McFarland, South Dakota State University, Brookings, SD.

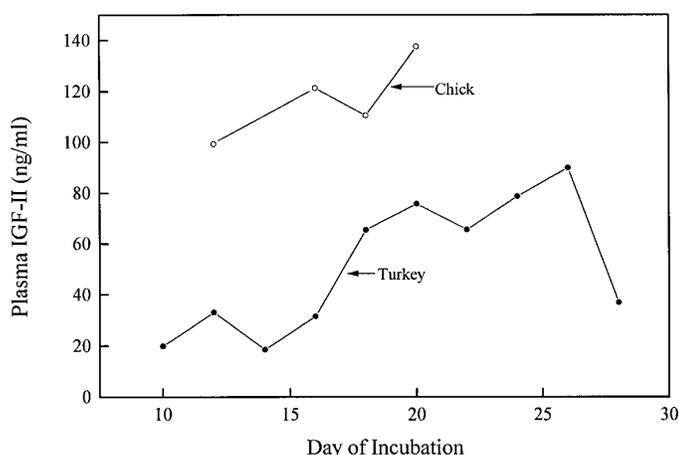


FIGURE 1 Profiles of plasma insulin-like growth factor-II during incubation of turkey and chick embryos (McMurtry, unpublished observations).

EMBRYO PLASMA IGF

Insulin-like growth factor-I gene expression can be detected soon after fertilization through d 8 in whole chick embryos (DePablo et al. 1990). Interestingly, IGF-I gene expression is not detectable in liver (Kikuchi et al. 1991) until after hatching, suggesting that circulating IGF-I is extrahepatic in origin in the developing avian embryo.

Blood IGF-I can be detected as early as d 6 in chick embryos and by d 10 in the turkey embryo, with levels peaking during the mid-incubation period. When embryos are incubated under shell-less conditions, the mid-incubation increase is absent, resulting in reduced growth (DePablo et al. 1991) and a general failure to thrive (McMurtry et al. 1996c).

Few studies have reported on the role of IGF-II in avian species. Insulin-like growth factor-II gene expression has been evaluated in 4-d-old chick embryos (Engstrom et al. 1987) as well as in differentiating turkey satellite cells (Ernst et al. 1996). We recently monitored circulating IGF-II levels in developing chick and turkey embryos utilizing a homologous radioimmunoassay for chicken IGF-II. In both species, IGF-II concentrations increased as incubation advanced (**Fig. 1**), with levels approximately 10-fold greater than for IGF-I, suggesting that IGF-II is an important functionary to embryonic development as in mammals (Stewart and Rotwein 1996).

INSULIN-LIKE GROWTH FACTORS IN EMBRYO DEVELOPMENT

Despite the early onset of tissue IGF-I gene expression and significant plasma concentrations during chick and turkey embryogenesis, the question remains whether IGF-I and IGF-II

are important regulators of embryonic growth and metabolism. The administration of IGF-I or an IGF-I analogue to chick embryos does not stimulate growth or enhance individual organ or tissue weights at hatching (McMurtry et al. 1995, Spencer et al. 1990). In contrast, others have reported that when administered early (d 2), IGF-I stimulates several growth (total protein) and metabolic indicators (creatine kinase and creatine-kinase MB) when evaluated 48 h later (DePablo et al. 1991). No studies have been reported on the effects of IGF-II administration to developing avian embryos.

The effects of IGF-I and IGF-II on various cell and tissue types derived from the avian embryo are multiple and diverse (McMurtry et al. 1997). Biological responses attributable to the IGF include stimulation of amino acid and glucose uptake, increased DNA synthesis, and stimulation of tissue growth. Clearly, the actions ascribed to the IGFs are significant to the overall regulation of the events of embryogenesis.

INSULIN-LIKE GROWTH FACTORS IN POSTHATCH DEVELOPMENT

Evidence for a relationship between the IGF and the regulation of posthatch growth in domestic fowl is less than convincing (Vasilatos-Younken and Scanes 1991). Tissue IGF-I gene expression is detectable throughout posthatch growth in chickens (Tanaka et al. 1996), with the liver being the major contributor to circulating IGF-I (Rosselot et al. 1995). Numerous studies have shown that circulating IGF-I increases with advancing age (McMurtry et al. 1997). In summary, the results of these studies strongly suggest that the relationship between circulating IGF-I and posthatch growth in poultry is highly variable (Vasilatos-Younken and Scanes 1991). In general, what has been reported to date suggests that genetic selection for increased growth rate in meat-type chickens has resulted in depressed IGF-I synthesis and secretion.

The biological action of IGF-I and -II has been investigated in tissues and cells derived from growing birds. This biological action includes, but is not limited to, increased glucose and amino acid uptake, enhanced DNA and protein synthesis, and stimulation of proliferation of various cell types (McMurtry et al. 1997).

Several attempts have been made to enhance growth rate and alter carcass fat composition in poultry by the administration of exogenous IGF, the results of which are summarized in **Table 1**. These observations suggest that the IGF may be more tightly coupled to intermediary metabolism rather than growth per se in domestic birds. Moreover, the evidence suggests that IGF are involved in some aspect of lipid metabolism in poultry (Goodridge et al. 1989).

Definitive information is lacking on whether IGF-II influences growth rate in domestic birds. It has been reported that plasma IGF-II concentrations are unrelated to growth rate in either dwarf or high growth rate lines of chickens (Scanes et

TABLE 1

Effect of exogenous IGF-I/-II on growth rate and body composition in chickens

Compound	Plasma growth factors	Growth effects	Body composition effects	Reference
h IGF-I	↑ IGF-I	None	↓ abdominal fat	Huybrechts et al. 1992
h IGF-I	↑ IGF-I	None	None	McGuinness and Cogburn, 1991
h IGF-I	↑ IGF-I	None	↓ abdominal fat	Tixier-Boichard et al. 1992
h IGF-II	↑ IGF-II	None	↑ abdominal fat	Spencer et al. 1996
anti-IGF-I/-II	↓ IGF-I/-II	Decrease	↓/↓ abdominal fat	Spencer et al. 1995

al. 1989). We recently monitored plasma IGF-II in growing chickens and turkeys and found no discernible relationship between IGF-II and any growth variables (Fig. 2).

Similar to the situation in mammals, in vivo the IGF are clearly involved in glucose and energy metabolism in birds. When administered to chickens as a bolus, IGF-I evoked significant changes in circulating metabolites, including depressed glucose and increased free fatty acids, uric acid and calcium (McMurtry et al. 1996a). Proportionally, more IGF (IGF-I + IGF-II) are present in the free form in birds than in mammals (McMurtry et al. 1997). It is of interest to speculate that the IGF are involved in establishing a blood glucose baseline, and any perturbations in glucose, such as postprandial increases, are resolved by insulin. The relatively higher concentrations of free IGF-I and -II in blood of chickens support such a hypothesis.

NUTRITION-INSULIN-LIKE GROWTH FACTOR INTERACTIONS

Given the importance of nutrition in growth and development, it is somewhat surprising that more information is not available on nutrient-IGF relationships in domestic poultry. The GH-IGF-I axis in domestic fowl seems to be differentially sensitive to alterations in the plane of nutrition. Food deprivation for 5 d depresses circulating IGF-I concentrations, and upon refeeding, concentration return to near initial concentrations (Kim et al. 1991, Morishita et al. 1993). However, in both studies complete restoration in blood IGF-I was not attained. Conversely, Kita et al. (1996) reported that a complete return to normal IGF-I was observed following restricted feeding, suggesting that the extent of nutrient deprivation determines the degree to which IGF-I synthesis and secretion return to normal following periods of nutrient modification. Contrary to the IGF-I response, IGF-II concentrations are increased following 24 h of food withdrawal in chickens (Fig. 3, and McMurtry et al. 1998). Hormone levels do not return to normal until after refeeding.

Dietary components have also been shown to alter circulating IGF-I. Plasma IGF-I is depressed in broiler chicks consuming a large calorie-to-protein ratio diet (Rosebrough et al. 1993). A diet reduced in protein (5% crude protein) depressed circulating IGF-I within 2 d, whereas changes in GH did not occur until d 8 compared with controls (Lauterio and Scanes

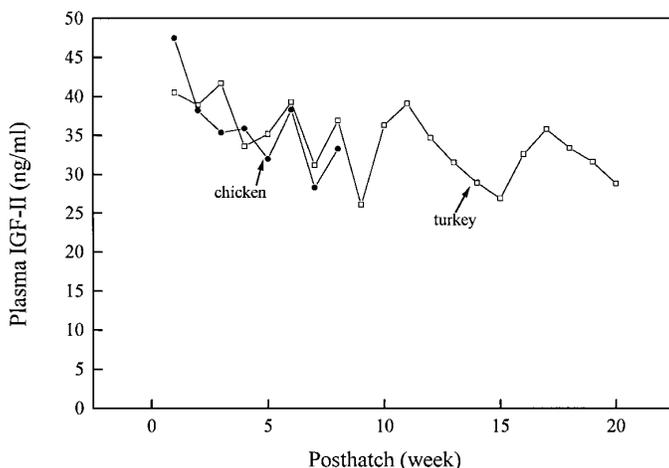


FIGURE 2 Profiles of plasma insulin-like growth factor-II during posthatch growth in male chickens and turkeys (McMurtry, unpublished observations).

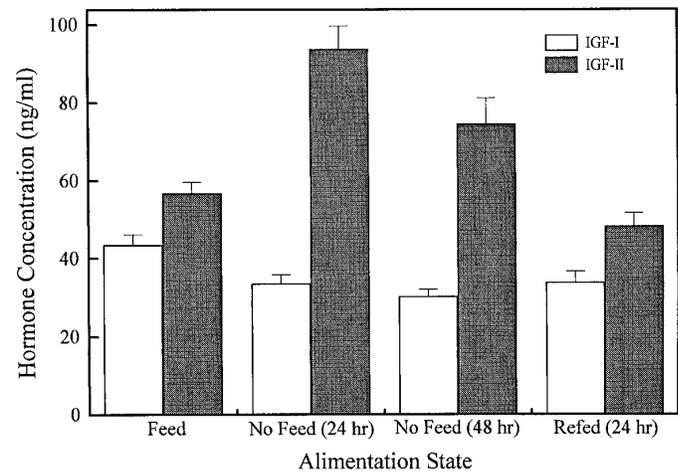


FIGURE 3 Effect of food withdrawal and refeeding on plasma IGF-II in male chickens (McMurtry, unpublished observations).

1987a and 1987b). However, feeding low protein diets to broiler chicks does not alter tissue IGF-I mRNA activity (Kita et al. 1996). Diets high in polyunsaturated fatty acids fed to young chicks increase IGF-I in plasma and liver but do not affect bone IGF-I concentrations (Watkins et al. 1996).

SUMMARY

In many ways, IGF physiology in birds is similar to that in other species. However, it is clear that several differences in IGF physiology exist between birds and mammals. For example, more IGF is present in the free form in chickens. To date, no unique IGF-II receptor has been identified in birds. Despite an increasing understanding of the IGF in avian species, several important questions remain. Does an IGF-II receptor entity exist in birds? How does nutrition affect IGF-I and -IGF-II gene expression, and can this information be used to enhance poultry production? Can the genetic variation present in poultry be utilized to positively modify IGF gene expression and physiology? What is the relationship between the IGF and the etiology of several disease states associated with rapid growth in poultry, including tibial dyschondroplasia, obesity, ascites and spiking mortality syndrome? Answers to these questions are relevant to our understanding of the basic mechanisms of IGF physiology and may assist in the amelioration of problems found in modern poultry production.

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