ELSEVIER

Domestic Animal Endocrinology 17 (1999) 181–190

DOMESTIC ANIMAL ENDOCRINOLOGY

New insights into the mechanism and actions of growth hormone (GH) in poultry

R. Vasilatos-Younken[a,*], X.-H. Wang[a], Y. Zhou[a], J. R. Day[b], J.P. McMurtry[d], R.W. Rosebrough[d], E. Decuypere[e], N. Buys[e], V. Darras[e], J.L. Beard[c], F. Tomas[f]

[a]*Department of Poultry Science, The Pennsylvania State University, University Park, PA 16802, USA,*
[b]*Department of Biology, The Pennsylvania State University, University Park, PA 16802, USA*
[c]*Department of Nutrition, The Pennsylvania State University, University Park, PA 16802, USA*
[d]*Growth Biology Laboratory, Livestock and Poultry Science Institute, USDA-ARS, Beltsville, MD 20705, USA*
[e]*Leuven Poultry Research Group, Catholic University of Leuven, Heverlee 3001, Belgium*
[f]*Cooperative Research Center for Tissue Growth and Repair, Adelaide, SA, Australia*

Received 5 February 1999; accepted 5 February 1999

Abstract

Despite well documented anabolic effects of GH in mammals, a clear demonstration of such responses in domestic poultry is lacking. Recently, comprehensive dose-response studies of GH have been conducted in broilers during late post-hatch development (8 to 9 weeks of age). GH reduced feed intake (FI) and body weight gain in a dose-dependent manner, whereas birds pair-fed to the level of voluntary FI of GH-infused birds did not differ from controls. The reduction in voluntary FI may involve centrally mediated mechanisms, as hypothalamic neuropeptide Y protein and mRNA were reduced with GH, coincident with the maximal depression in FI. Growth of breast muscle was also reduced in a dose-dependent manner. Circulating IGF-I was not enhanced by GH, despite evidence that early events in the GH signaling pathway were intact. A GH dose-dependent increase in circulating 3,3′,5-triiodothyronine(T3) paralleled decreases in hepatic 5D-III monodeiodinase activity, whereas 5′D-I activity was not altered. This confirms that a marked hyperthyroid response to GH occurs in late posthatch chickens, resulting from a decrease in the degradative pathway of T3 metabolism. This secondary hyperthyroidism would account for the decreased skeletal muscle mass (52) and lack of enhanced IGF-I (53) in GH-treated birds. Based upon these studies, it is now evident that GH does in fact have significant effects in poultry, but metabolic responses may confound the anabolic potential of the hormone. © 1999 Elsevier Science Inc. All rights reserved.

* Corresponding author. Tel.: +1-814-865-4642; fax: +1-814-865-5691.
E-mail address: rxv@psu.edu (R. Vasilatos–Younken)

0739-7240/99/$ – see front matter © 1999 Elsevier Science Inc. All rights reserved.
PII: S0739-7240(99)00035-1

Keywords: Growth hormone; Poultry; Muscle; Thyroid hormones

1. Introduction

It is well documented that growth hormone (GH) administration to red meat animals, in particular swine, consistently improves growth performance including average daily gain and feed efficiency, with marked changes in the composition of gain characterized by enhanced muscle growth and reduced adipose tissue deposition [1–6]. In fact, the mass of individual muscles is reported to increase almost 50%, and carcass fat content to decrease by as much as 75% with exogenous GH treatment to pigs [7]. The anabolic response to GH is associated with increased rates of fractional protein synthesis in both liver and skeletal muscle [12,13], consistent with increased RNA content of these tissues [14,5,13] and reflected in increased rates of amino acid accretion into tissue protein [15]. In all cases, muscle fiber hypertrophy occurs with no change in fiber number when GH is administered postnatally [8–11]. It should be recognized that the muscle anabolic response to GH seems to be maximal at relatively low dosages of the hormone in swine, whereas reductions in carcass fat and in vivo increases in circulating insulin-like growth factor 1 (IGF-1) continue to increase in a dose-responsive manner, even at the highest dosages of GH evaluated in the above and other studies [3,8].

It is generally accepted that the anabolic responses to GH in mammals are mediated by IGF-1, which stimulates myoblast and satellite cell proliferation and terminal myogenic differentiation, the latter effect involving induction of myogenic genes (see [16 and 17] for comprehensive reviews). Satellite cells are important for myofiber hypertrophy and for regeneration of muscle tissue postnatally, and IGF-1 can enhance growth of avian myogenic cells in vitro. Physiological concentrations of IGF-1 markedly stimulated thymidine incorporation into DNA in cultured chicken satellite cells [18,19], and in combination with fibroblast growth factor (FGF), stimulated proliferation of turkey satellite cells [20]. Insulin-like growth factor-1 also stimulated Brd-U-labeling of nuclei in satellite cells from sex-linked dwarf (SLD) chickens, which express low circulating levels of IGF-1 due to a defect in tissue GH receptors [21]. In addition, IGF-1 but not GH stimulated amino acid transport and protein synthesis, and inhibited protein degradation in chicken skeletal muscle satellite cells [22].

In vivo, exogenous IGF-1 has been reported to cause modest enhancement of overall somatic [69] but no enhancement of skeletal muscle growth in either normal [23,24,69] or SLD [24] chickens. However, free IGF-1 (i.e., not bound to IGF binding proteins) is rapidly cleared from the circulation, and less likely to be available to peripheral tissues such as skeletal muscle in comparison to more highly perfused visceral organs [25]. In fact, where increased somatic growth has been reported for the chicken, gross changes in tissue deposition were proportionately greatest in the gut [69]. In some cases, IGF-1 administered to chickens was associated with reduced skeletal muscle mass [24,26], likely due to depressed circulating concentrations of insulin (a potent inhibitor of proteolysis) [26].

Although most tissues synthesize IGF-1 locally, circulating IGF-1 is believed to be

derived primarily from the liver in response to GH, and acts upon other tissues in an endocrine manner. Circulating concentrations of IGF-1 are substantially reduced (but not completely ablated) in hypophysectomized [27–29] and SLD chickens [30–32], and hepatic IGF-1 mRNA is undetectable in the SLD [32], supporting the hepatic origin of most circulating IGF-1, and the GH-dependence of IGF-1 synthesis by the liver in poultry.

Although overexpression of IGF-1 in striated muscle of transgenic mice was demonstrated to produce marked hypertrophy of muscle fibers [34], the prevailing consensus concerning IGF-1-mediated anabolic responses to exogenous GH in mammals is that these are a function of circulating IGF-1 acting in an endocrine manner, rather than IGF-1 produced locally by tissues such as skeletal muscle and acting in an autocrine/paracrine manner. In pigs administered exogenous GH, circulating IGF-1 concentrations are consistently increased and are GH dose-responsive [3,4,13,33], whereas specific muscles such as the longissimus exhibit myofiber hypertrophy with no increase in tissue IGF-1 mRNA expression [33], supporting an endocrine route for IGF-1 action.

In general, exogenous GH administration using both recombinant and pituitary-derived homologous preparations, have failed to improve somatic growth, and, in particular, skeletal muscle deposition, in pituitary-intact domestic poultry [35–43]. In all the above studies, only one or two dosages of GH were explored, and ranged from low physiological [35] to pharmacological [43]. Also relevant to the lack of an anabolic response to GH in domestic poultry is that little or no significant response to GH in terms of enhancement of circulating IGF-1 concentrations have been obtained in immature, growing birds [39–42,44]. This is particularly surprising in that hepatic GH receptor (GH-R) gene expression is detectable beginning at early ages in the chicken [45,46], in vivo administration of GH increases hepatic IGF-1 mRNA and protein content [44], and GH stimulates IGF-1 synthesis and its release into the medium by chicken hepatocytes in culture [47]. These suggest all steps in the pathway necessary for a circulating IGF-1 response to GH in vivo are functional in the chicken (for review, see [55]).

Our laboratory recently completed an extensive GH dose-response study which has enabled us to gain new insights into the mechanism and actions of GH in poultry (54,59, Vasilatos-Younken et al., unpublished data). Briefly, recombinant chicken GH (cGH) (0, 10, 50, 100 or 200 μg/kg BW/day; 0GH, 10GH, 50GH, 100GH, and 200GH) was administered for 7 days (from 8 to 9 wk of age) to female broiler-strain chickens ($n = 10$ per dosage) during late posthatch development when endogenous GH secretion is relatively low. Each daily dose was delivered by means of iv infusion in a physiologically appropriate pattern of 16 equal pulses (one every 90 min), to mimic the normal endogenous pulse pattern of GH secretion in the growing chicken. The dosages administered resulted in circulating concentrations of GH over the full physiological range found in the broiler during posthatch development (i.e., from <1.0 ng/mL to >100 ng/mL).

2. Results and discussion

In contrast to the positive effects of exogenous GH on BW gain in mammals, cGH administered to late posthatch broiler-strain chickens reduced body weight gain in a dose-

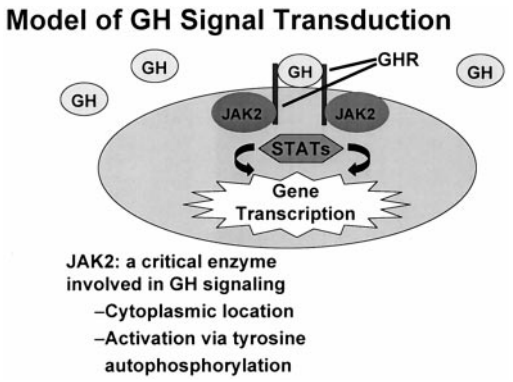

Fig. 1. Model of the presumed growth hormone (GH) signaling pathway related to transcriptional regulation of GH-responsive genes. Signaling is initiated by binding of GH to adjacent receptors (GHR) to form a functional GHR-GH-GHR dimer, and bringing about a conformational change in the GHR. This results in association of a member of the Janus family of tyrosine kinases (JAK2) with the GHR, and tyrosine phosphorylation of the GHR and autophosphorylation of JAK2, which further recruits members of the STAT family of transcriptional regulators. STAT proteins (including STATs 1, 3, and 5) are activated in response to phosphorylation by JAK2, and translocated to the nucleus where they regulate transcription of GH-responsive genes.

dependent manner, with a maximal depression (34%) at the highest dosage administered (200 GH). Feed intake (FI) was also maximally depressed (19%) at this dosage; however, depressed somatic growth was not secondary to the reduction in FI, as BW gains for birds pair-fed to the level of voluntary FI of the GH-infused birds, but administered only vehicle, did not differ from controls. Reductions in voluntary FI in response to GH may involve centrally mediated mechanisms, as hypothalamic neuropeptide Y protein and gene expression (mRNA) were reduced approximately 34 and 50%, respectively, and hypothalamic epinephrine was reduced 37% at the maximal depression in FI with 200GH, whereas pair-fed birds did not differ from controls [54]. Neuropeptide Y is a potent stimulator of FI, and has a robust stimulatory effect in the chicken when administered intracerebroventricularly [48]. Most of the effects of NPY seem to be mediated by neurons of the hypothalamus [49,50], and the extensive coexistence of NPY and monoamines in the CNS suggests that these may interact in the hypothalamus to regulate FI [51]. Given that most of the NPY-containing neurons in the arcuate nucleus express GH-R mRNA [56], and GH can cross the blood-brain barrier [57], it is possible that GH acts directly to alter hypothalamic NPY and, hence, FI. These data provide new evidence of a role for GH in altering voluntary FI via centrally mediated mechanisms, independent of its effects as a repartitioning agent.

Although the complete signal transduction pathway for GH has not been fully delineated, several signaling events are known to occur after binding of GH to target tissue receptors and formation of a GH-GH-R dimer (see [58] for review of molecular mechanisms of GH action). These include recruitment of a member of the Janus-activated kinase family, JAK2 tyrosine kinase. JAK2 binds to the GH-R, is autophosphorylated, and results in tyrosine phosphorylation of the GH-R and a variety of cytosolic substrates including several members of the STAT family of transcriptional regulators. The latter subsequently translocate to the nucleus, bind to DNA, and activate transcription of specific genes (Figure 1). Hepatic JAK2 protein

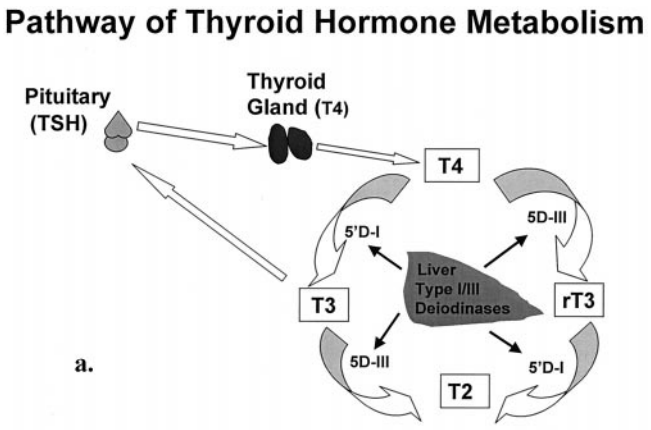

Fig. 2. (a) Normal pathway of thyroid hormone metabolism. The metabolically active form of thyroid hormone, 3,3′,5-triiodo-1-thyronine (T_3), is derived primarily via peripheral (hepatic) deiodination of thyroxine (T_4) by 5′D-I monodeiodinase (5′D-I). Degradation of both T_4 (to rT_3) and T_3 (to T_2) are effected by 5D-III deiodinase (5D-III). Thyroxine production by the thyroid gland is directly regulated by pituitary thyroid-stimulating hormone (TSH), which is responsive to feedback regulation from circulating T_3. (b) Effect of growth hormone (GH) on thyroid hormone metabolism. Growth hormone decreases the activity of hepatic 5D-III deiodinase, resulting in reduced degradation of both T_3 and T_4, and increasing circulating T_3 concentrations. Increased circulating T_3 is presumed to feedback to reduce pituitary TSH secretion and, consequently, production of T_4 by the thyroid gland, with a net effect of reduced circulating T_4.

and tyrosine phosphorylation were increased in a curvilinear, dose-dependent manner with cGH administration, with a maximal response at 100 GH for both [59]. Hepatic IGF-1 protein concentration was also increased from virtually undetectable levels to over 60- to 70-fold with cGH [59]. However, despite evidence that early events in the GH signaling pathway were intact, and hepatic IGF-1 synthesis was stimulated by cGH, circulating IGF-1 concentrations were not altered by cGH at any dosage. Although failure of exogenous GH to enhance circulating IGF-1 levels would predictably limit an anabolic response to the hormone, actual decreased BW gain suggests other mechanisms are at play. In fact, skeletal (breast) muscle deposition was also reduced by cGH in a dose-dependent, curvilinear manner, with a maximal reduction (13%) in mass at 100 GH. Assessment of skeletal muscle free 3-methylhistidine content indicated no differences from control values with GH treatment, suggesting that proteolysis was not increased and the observed decrease in breast muscle mass was a function of a reduced rate of synthesis, also contrary to the known effects of exogenous GH as mediated by IGF-1 in mammals.

To begin to understand how administration of exogenous cGH to late posthatch chickens not only failed to enhance growth, but resulted in apparent catabolic tissue and conflicting endocrine responses, it must be realized that GH also has profound metabolic effects which, in avian species, are intimately tied to the thyrotropic axis (for review, see [60]). In birds, as in most species, 3,3′,5-triiodo-L-thyronine (T_3) is the metabolically active form of thyroid hormone, and is derived primarily from peripheral (largely hepatic) monodeiodination of thyroxine (T_4) by 5′D-I monodeiodinase, whereas degradation of both T_3 (to the inactive form, T_2) and T_4 (to rT_3) are effected by 5D-III deiodinase (Figure 2A). Growth hormone is

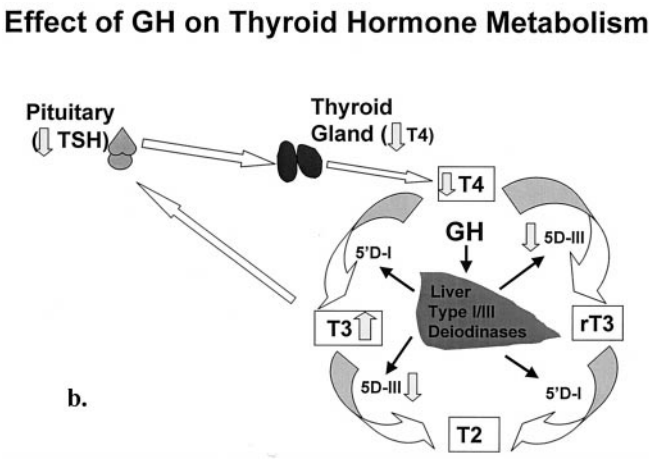

Fig. 2b.

reported to decrease hepatic 5D-III activity in the chicken, thereby decreasing T_3-degrading activity in the periphery and resulting in elevated circulating T_3 concentrations [61,62] (Figure 2B). This effect is developmentally regulated, as a hyperthyroid response to exogenous GH occurs in late embryonic development and in the newly hatched chick, but disappears during the early posthatch period, likely due to masking by high endogenous GH (and, T_3) status, and is reported to occur again in the adult bird [61,62,66].

Consistent with reported effects of acute GH administration on circulating thyroid hormones, GH increased plasma T_3 concentrations in a dose-dependent, curvilinear manner ($P < 0.001$), with a maximal (twofold) increase at 100 GH, but with no effect on 5′D-I. This T_3 response inversely paralleled dose-dependent decreases in hepatic 5D-III deiodinase activity ($p < 0.01$) and muscle mass, suggesting direct relationships among all three. These findings verify the expression of a marked hyperthyroid effect of GH in late posthatch chickens resulting from decreased peripheral degradation of circulating T_3, and strongly suggest that the apparent decreased body weight gain and, specifically, muscle mass in GH-treated birds is secondary to a GH-induced hyperthyroid state, and not a primary GH-lesion. Net skeletal muscle catabolism due to decreased muscle protein synthesis occurs with untreated thyrotoxicosis [52], and supplemental T_3 has been reported to reduce body weight gain in chickens [63–65].

Although factors regulating hepatic IGF-1 synthesis and release (beyond GH) are not well delineated, there is evidence that thyroid hormones may be critical regulators of IGF-1. Triiodothyronine alters IGF-1 production by neuronal cells in culture [67]; thyroid status profoundly influences circulating IGF-1 bioactivity and local IGF-1 production in a tissue-specific manner in the rat [68]; and circulating IGF-1 concentrations were reported to decrease in chickens administered supplemental T_3 [53,63]. Thus, the combined suppression of a GH-induced increase in circulating IGF-1 concentrations, together with the catabolic effects of GH-induced hyperthyroidism, preclude any potential for the anabolic effects of GH to be realized under conventional treatment regimes.

In summary, it is clear that GH does in fact have significant, dose-dependent effects in

avian species, but profound metabolic responses to the hormone, particularly with respect to the thyrotropic axis, may confound the realization of any IGF-1-mediated anabolic potential of GH in the growing bird. Further studies to delineate the regulation of hepatic IGF-1 release will help to verify if suppression of this event by exposure to relatively high levels of T_3 occurs, and potentially clarify the mechanism(s) of this action.

References

[1] Chung CS, Etherton TD, Wiggins JP. Stimulation of swine growth by porcine growth hormone. J Anim Sci 1985;60:118–30.
[2] Etherton TD, Wiggins JP, Chung CS, Evock CM, Rebhun JF, Walton PE. Stimulation of pig growth performance by porcine growth hormone and growth hormone releasing factor. J Anim Sci 1986;63:1389–1399.
[3] Etherton TD, Wiggins JP, Evock CM, et al. Stimulation of pig growth performance by porcine growth hormone: determination of the dose-response relationship. J Anim Sci 1987;64:433–43.
[4] Campbell RG, Steele NC, Caperna TJ, McMurtry JP, Solomon MB, Mitchell AD. Interrelationships between sex and exogenous growth hormone administration on performance, body composition and protein and fat accretion of growing pigs. J Anim Sci 1989;67:177–86.
[5] Evock CM, Caperna TJ, Steele NC, McMurtry JP, Rosebrough RW. Influence of time of injection of recombinant porcine somatotropin (rpST) relative to time of feeding on growth performance, hormone and metabolite status, and muscle RNA, DNA, and protein in pigs. J Anim Sci 1991;69:2443–51.
[6] Fabry J, Demeyer D, Thielemans MF, Deroanne C, Van de Voorde G, Deroover E, Dalrymple RH. Evaluation of recombinant porcine somatotropin on growth performance, carcass characteristics, meat quality, and muscle biochemical properties of belgian landrace pigs. J Anim Sci 1991;69:4007–18.
[7] Thiel LF, Beermann DH, Krick BJ, Boyd RD. Dose-dependent effects of exogenous porcine somatotropin on the yield, distribution, and proximate composition of carcass tissues in growing pigs. J Anim Sci 1993;71:827–35.
[8] Beerman DH, Fishell VK, Roneker K, Boyd RD, Armbruster G, Souza L. Dose-response relationships between porcine somatotropin, muscle composition, muscle fiber characteristics and pork quality. J Anim Sci 1991;68:2690–7.
[9] Soloman MB, Caperna TJ, Mroz RJ, Steele NC. Influence of dietary protein and recombinant porcine somatotropin administration in young pigs: III. Muscle fiber morphology and shear force. J Anim Sci 1994;72:615–21.
[10] Ono Y, Solomon MB, Evock-Clover CM, Steele NC, Maruyama K. Effects of porcine somatotropin administration on porcine muscles located within different regions of the body. J Anim Sci 1995;73:2282–8.
[11] Sorenson MT, Oksbjerg N, Agergaard N, Petersen JS. Tissue deposition rates in relation to muscle fibre and fat cell characteristics in lean female pigs (sus scrofa) following treatment with porcine growth hormone (pGH). Comp Biochem Physiol 1996;113:91–6.
[12] Eisenman HH, Hammond AC, Rumsey TS. Tissue protein synthesis and nucleic acid concentrations in steers treated with somatotropin. Br J Nutr 1989;62:657–71.
[13] Seve B, Ballevre O, Ganier P, Noblet J, Prugnaud J, Obled C. Recombinant porcine somatotropin and dietary protein enhance protein synthesis in growing pigs. J Nutr 1993;123:529–40.
[14] Pell JM, Bates PC. Collagen and non-collagen protein turnover in skeletal muscle of growth hormone-treated lambs. J Endocrinol 1987;115:R1–4.
[15] Caperna TJ, Campbell RG, Ballard RM, Steele NC. Somatotropin enhances the rate of amino acid deposition but has minimal impact on amino acid balance in growing pigs. J Nutr 1995;125:2104–13.
[16] Florini JR, Ewton DZ, Coolican SA. Growth hormone and the insulin-like growth factor system in myogenesis. Endocr Rev 1996;17:481–517.

[17] Dodson MV, Allen RE, Hossner KL. Ovine somatomedin, multiplication-stimulating activity, and insulin promote skeletal muscle satellite cell proliferation in vitro. Endocrinology 1985;117:2357–63.
[18] Duclos MJ, Wilkie RS, Goddard C. Stimulation of DNA synthesis in chicken muscle satellite cells by insulin and insulin-like growth factors: evidence for exclusive mediation by a type-I insulin-like growth factor receptor. J Endocrinol 1991;128:35–42.
[19] Wilkie RS, O'Neill IE, Butterwith SC, Duclos MJ, Goddard C. Regulation of chick muscle satellite cells by fibroblast growth factors: interaction with insulin-like growth factor-I and heparin. Growth Regul 1995;5: 18–27.
[20] McFarland DC, Pesall JE, Gilkerson KK. The influence of growth factors on turkey embryonic myoblasts and satellite cells in vitro. Gen Comp Endocrinol 1993;89:415–24.
[21] Goddard C, Johnson R, Gilhooley HJ, Gardener JO, Gray A, Wilkie RS, Butterwith SC. Decreased muscle cell proliferation in chicks with a deletion in the GH receptor gene. J Mol Endocrinol 1996;17:67–78.
[22] Duclos MJ, Chevalier B, Goddard C, Simon J. Regulation of amino acid transport and protein metabolism in myotubes derived from chicken muscle satellite cells by insulin-like growth factor-I. J Cell Physiol 1993;157:650–7.
[23] Huybrechts LM, Decuypere E, Buyse J, Kuhn ER, Tixier-Boichard M. Effect of recombinant human insulin-like growth factor-I on weight gain, fat content and hormonal parameters in broiler chickens. Poultry Sci 1992;71:181–7.
[24] Tixier-Boichard M, Huybrechts LM, Decuypere E, et al. Effects of insulin-like growth factor-I (IGF-I) infusion and dietary triiodothyronine (T3) supplementation on growth, body composition and plasma hormone levels in sex-linked dwarf mutant and normal chickens. J Endocrinol 1992;133:101–10.
[25] Mathews LS, Hammer RE, Behringer RR, et al. Growth enhancement of transgenic mice expressing human insulin-like growth factor-I. Endocrinology 1988;123:2827–33.
[26] Czerwinski SM, Cate JM, Francis G, Tomas F, Brocht DM, McMurtry JP. The effect of insulin-like growth factor-I (IGF-I) on protein turnover in the meat-type chicken (*Gallus domesticus*). Comp Biochem Physiol 1988;119C:75–80.
[27] Scanes CG, Duyka DR, Lauterio TJ, Bowen SJ, Huybrechts LM, Bacon WL, King DB. Effect of chicken growth hormone, triiodothyronine and hypophysectomy in growing domestic fowl. Growth 1986;50:12–31.
[28] Lazarus DD, Scanes CG. Acute effects of hypophysectomy and administration of pancreatic and thyroid hormones on circulating concentrations of somatomedin-C in young chickens: relationship between growth hormone and somatomedin-C. Domest Anim Endocrinol 1988;5:283–9.
[29] Proudman JA, Cogburn LA, McGuinness MC, Krishnan KA. Endocrine responses of hypophysectomized turkey poults given daily injection of chicken growth hormone. Poultry Sci 1989;68(suppl):116.
[30] Scanes CG, Dunnington EA, Buonomo FC, Donoghue DJ, Siegel PB. Plasma concentrations of insulin like growth factors (IGF-) I and IGF-II in dwarf and normal chickens of high and low weight selected lines. Growth Dev Aging 1989;53:151–7.
[31] Vasilatos-Younken R, Dunnington EA, Siegel PB, McMurtry JP. Tissue-specific alterations in insulin-like growth factor-I concentrations in response to 3,3′, 5-triiodo-l-thyronine supplementation in the growth hormone receptor-deficient sex-linked dwarf chicken. Gen Comp Endocrinol 1997;105:31–9.
[32] Tanaka M, Hayashida Y, Sakaguchi K, et al. Growth hormone-independent expression of insulin-like growth factor I messenger ribonucleic acid in extrahepatic tissues of the chicken. Endocrinology 1996;137: 30–4.
[33] Coleman ME, Russell L, Etherton TD. Porcine somatotropin (pST) increases IGF-I mRNA abundance in liver and subcutaneous (s.c.) adipose tissue but not in skeletal muscle of growing pigs. J Anim Sci 1994;72:918–24.
[34] Coleman ME, DeMayo F, Yin KC, et al. Myogenic vector expression of insulin-like growth factor I stimulates muscle cell differentiation and myofiber hypertrophy in transgenic mice. J Biol Chem 1995;270: 12109–16.
[35] Leung FC, Taylor JE, Wien S, Iderstine AV. Purified chicken growth hormone (GH) and a human pancreatic GH-releasing hormone increase body weight gain in chickens. Endocrinology 1986;118:1961–5.

[36] Burke WH, Moore JA, Ogez JR, Builder SE. The properties of recombinant chicken growth hormone and its effects on growth, body composition, feed efficiency, and other factors in broiler chickens. Endocrinology 1987;120:651–8.
[37] Vasilatos-Younken R, Cravener TL, Cogburn LA, Mast MG, Wellenreiter RH. Effect of pattern of administration on the response to exogenous, pituitary-derived chicken growth hormone by broiler-strain pullets. Gen Comp Endocrinol 1988;71:268–83.
[38] Cravener TL, Vasilatos-Younken R. Effect of s.c. infusion of pituitary-derived chicken growth hormone on growth performance of broiler pullets. Poultry Sci 1989;68:1133–40.
[39] Cogburn LA, Liou SS, Rand AL, McMurtry JP. Growth, metabolic and endocrine responses of broiler cockerels given a daily s.c. injection of natural or biosynthetic chicken growth hormone. J Nutr 1989;119: 1213–22.
[40] Rosebrough RW, McMurtry JP, Vasilatos-Younken R. Effect of pulsatile or continuous administration of pituitary-derived chicken growth hormone (p-cGH) on lipid metabolism in broiler pullets. Comp Biochem Physiol 1991;99A:207–14.
[41] Bacon WL, Long DW, Vasilatos-Younken R. Responses to exogenous pulsatile turkey growth hormone by growing 8-week-old female turkeys. Comp Biochem Physiol 1995;111B:471–82.
[42] Moellers R F, Cogburn LA. Chronic intravenous infusion of chicken growth hormone increases body fat content of young broiler chickens. Comp Biochem Physiol 1995;110A:47–56.
[43] Radecki SV, McCann-Levorse L, Agarwal SK, Burnside J, Proudman JA, Scanes CG. Chronic administration of growth hormone (GH) to adult chickens exerts marked effects on circulating concentrations of insulin-like growth factor-I (IGF-I), IGF binding proteins, hepatic GH regulated gene I, and hepatic GH receptor mRNA. Endocrine 1997;6:117–24.
[44] Rosselot G, McMurtry JP, Vasilatos-Younken R, Czerwinski S. Effect of exogenous chicken growth hormone (cGH) administration on insulin-like growth factor-I (IGF-I) gene expression in domestic fowl. Mol Cell Endocrinol 1995;114:157–66.
[45] Burnside J, Cogburn LA. Developmental expression of hepatic growth hormone receptor and insulin-like growth factor-I mRNA in the chicken. Mol Cell Endocrinol 1992;89:91–6.
[46] Oldham ER, Bingham B, Baumbach WR. A functional polyadenylation signal is embedded in the coding region of chicken growth hormone receptor RNA. Mol Endocrinol 1993;7:1379–90.
[47] O'Neill IE, Houston B, Goddard C. Stimulation of insulin-like growth factor I production in primary cultures of chicken hepatocytes by chicken growth hormone. Mol Cell Endocrinol 1990;70:41–7.
[48] Kuenzel WJ, Snapir N, Rexroad CE Jr. Food intake and biogenic amine concentrations in brain regions of chicks following intracerebroventricular injection of 6-hydroxydopamine. Pharmacol Biochem Behav 1987; 27:257–63.
[49] Leibowitz SF. Hypothalamic neuropeptide Y, galanin, and amines. Concepts of coexistence in relation to feeding behavior. Ann NY Acad Sci 1989;575:221–33.
[50] Sahu A, Kalra PS, Kalra SP. Food deprivation and ingestion induce reciprocal changes in neuropeptide Y concentrations in the paraventricular nucleus. Peptides 1988;9:83–6.
[51] Sawchenko PE, Swanson LW, Grzanna R, Howe PR, Bloom SR, Polak JM. Co-localization of neuropeptide Y immunoreactivity in brainstem catecholaminergic neurons that project to the paraventricular nucleus of the hypothalamus. J Comp Neurol 1985;241:138–53.
[52] Morrison WL, Gibson JNA, Jung RT, Rennie MJ. Skeletal muscle and whole body protein turnover in thyroid disease. Eur J Clin Invest 1988;18:62–8.
[53] Vasilatos-Younken R, Dunnngton EA, Siegel PB, McMurtry JP. Tissue-specific alterations in insulin-like growth factor-1 concentrations in response to 3,3′,5-triiodo-L-thyronine supplementation in the growth hormone-receptor deficient sex-linked dwarf chicken. Gen Comp Endocrinol 1997;105:31–9.
[54] Wang XH, Day JR, Beard JL, Zhou Y, Vasilatos-Younken R. Evidence for mediation of the appetite-depressive effect of growth hormone (GH) on voluntary feed intake (FI) by neuropeptide Y (NPY) and monoamines. Poultry Sci 1998;77(suppl 1):33, No. 124.
[55] Vasilatos-Younken R. Absence of growth hormone-induced avian muscle growth in vivo. Poultry Sci 1999;78:759–768.

[56] Chan YY, Steiner RA, Clifton DK. Regulation of hypothalamic neuropeptide Y neurons by growth hormone in the rat. Endocrinology 1996;137:1319–25.
[57] Tannebaum GS, Ling N. The interrelationship of growth hormone (GH)-releasing factor and somatostatin in generation of the ultradian rhythm of GH secretion. Endocrinology 1980;115:1952–7.
[58] Carter-Su C, Schwartz J, Smit, LS. Molecular mechanism of growth hormone action. Annu Rev Physiol 1996;58:187–207.
[59] Zhou Y, Wang X-H, McMurtry JP, Vasilatos-Younken R. Induction and activation of JAK2 protein occur with chronic exposure to GH, despite lack of an anabolic response in chicken skeletal muscle. Poultry Sci 1988;77(suppl 1):33, No. 124.
[60] Kuhn ER, Berghman LR, Moons L, Vandesande F, Decuypere E, Darras VM. Hypothalamic and peripheral control of thyroid function during the life cycle of the chicken. In: Sharpe PJ, editor. Avian endocrinology. Bristol: J Endocrinol Ltd., 1993. p. 29–46.
[61] Darras VM, Rudas P, Visser TJ, et al. Endogenous growth hormone controls high plasma levels of 3,3′,5-triiodothyronine (T_3) in growing chickens by decreasing the T_3-degrading Type III deiodinase activity. Domest Anim Endocrinol 1993;10:55–65.
[62] Darras VM, Berghman LR, Vanderpooten A, Kuhn ER. Growth hormone acutely decreases type III iodothyronine deiodinase in chicken liver. FEBS 1992;310:5–8.
[63] Tixier-Boichard M, Decuypere E, Huybrechts L, Kuhn E, Perat M. Effects of dietary T_3 on growth parameters and hormone levels in normal and sex-linked dwarf chickens. Domest Anim Endocrinol 1990;7:573–86.
[64] Bowen SJ, Huybrechts LM, Marsh JA, Scanes CG. Influence of triiodothyronine and growth hormone on growth of dwarf and normal chickens: interactions of hormones and genotype. Comp Biochem Physiol 1987;86A:137–42.
[65] May JD. Effect of dietary thyroid hormone on growth and feed efficiency of broilers. Poultry Sci 1980;59:888–92.
[66] Darras VM, Huybrechts LM, Berghman L, Kuhn ER, Decuypere E. Ontogeny of the effect of purified chicken growth hormone on the liver 5′ monodeiodination activity in the chicken: reversal of the activity after hatching. Gen Comp Endocrinol 1990;77:212–20.
[67] Binoux M, Faivre-Bauman A, Lassarre C, Barret A, Tixier-Vidal A. Triiodothyronine stimulates the production of insulin-like growth factor (IGF) by fetal hypothalamus cells cultured in serum-free medium. Dev Brain Res 1985;21:19–321.
[68] Thomas MR, Miell JP, Taylor AM, et al. Endocrine and cardiac paracrine actions of insulin-like growth factor-I (IGF-I) during thyroid dysfunction in the rat: is IGF-I implicated in the mechanism of heart weight/body weight change during abnormal thyroid function? J Mol Endocrinol 1993;10:313–23.
[69] Tomas FM, Pym RA, McMurtry JP, Francis GL. Insulin-like growth factor (IGF)-I but not IGF-II promotes lean growth and feed efficiency in broiler chickens. Gen Comp Endo 1998;110:262–75.