# 2 Regulation of Insulin-Like Growth Factor-I by Nutrition

*Jean-Paul Thissen, Véronique Beauloye, Jean-Marie Ketelslegers, and Louis E. Underwood*

## KEY POINTS

- Nutrition is one of the principal regulators of circulating IGF-I. Many mechanisms are involved in the nutritional regulation of IGF-I.
- Both energy and protein are critical to the regulation of serum IGF-I concentrations. After fasting, adequate energy and protein are necessary for restoration of serum IGF-I, but energy may be somewhat more important than protein. While a low intake of protein is able to increase IGF-I in the presence of adequate energy, there is a threshold requirement of energy below which optimal protein intake fails to raise IGF-I after fasting.
- The decline of serum IGF-I during dietary restriction is independent of diet-induced alterations in pituitary GH secretion. In severe dietary restriction (fasting), a marked decrease in the number of liver somatogenic receptors suggests that a GH receptor defect is involved in the decline of serum IGF-I. In protein restriction, the decline of serum IGF-I results from a postreceptor defect in GH action at the hepatic level.
- Nutritional deprivation decreases hepatic IGF-I production by diminishing IGF-I gene expression. Decline in IGF-I gene expression results from both transcriptional and post-transcription mechanisms.
- Diet restriction also increases the clearance and degradation of serum IGF-I through changes in the levels of circulating IGFBPs.
- The molecular mechanisms leading to the decline of IGF-I in catabolic stress seem to be similar to those operational in food deprivation.
- Nutrients may also control the biological action of IGF-I, either directly or indirectly, through changes in IGFBPs.

## 1. INTRODUCTION

Starvation causes growth arrest and decreases body cell mass. Although secondary changes in the hormonal milieu play a major role, the mechanisms by which insufficient nutrition cause growth retardation are not well elucidated. Given its stimulatory

From: *IGF and Nutrition in Health and Disease*
Edited by: M. S. Houston, J. M. P. Holly, and E. L. Feldman © Humana Press Inc., Totowa, NJ

effect on cell proliferation and differentiation and its anabolic effect on protein metabolism *(1)*, the decline in insulin-like growth factor (IGF)-I in states of undernutrition likely contributes to the observed growth arrest and loss of cell mass observed. In this chapter, we will review the mechanisms responsible for the decrease of IGF-I in response to fasting and food deprivation and compare the responses to insufficient nutrition to those that occur during critical illness *(2)*.

## 2. EVIDENCE FOR THE NUTRITIONAL REGULATION OF IGF-I IN HUMANS

### *2.1. Fasting and Malnutrition*

Fasting among normal volunteers causes serum IGF-I to begin to decline within 24 h and to reach 20% of prefast values by 10 d *(3)*. Changes in serum IGF-I concentrations parallel changes in nitrogen balance, suggesting that decreased IGF-I might mediate a decline in protein synthesis or an increase in protein breakdown. Decreased serum IGF-I is not restricted to fasting but also is observed in protein calorie malnutrition (marasmus, kwashiorkor, anorexia nervosa, celiac disease, AIDS, inflammatory bowel diseases) *(4)*. In general, the magnitude of IGF-I reduction relates to the severity of the nutritional insult as reflected by serum albumin concentrations, weight deficit, or loss of body cell mass. The sensitivity of serum IGF-I to nutrient deprivation and repletion makes it a useful marker of nutritional status (reviewed in Chapter 4). Growth hormone (GH) secretion often is increased in malnourished patients, suggesting that they have resistance to the action of GH *(5)*. The injection of pharmacological doses of GH, however, may still increase IGF-I and cause nitrogen retention in some malnourished patients *(6)*.

Serious illness is also associated with low circulating concentrations of IGF-I despite augmented GH concentrations *(7)*. This rise in GH secretion persists despite the calorie and protein supply afforded by artificial feeding, indicating that nutrient deprivation is not always responsible for the GH resistance observed in such patients.

### *2.2. Respective Roles of Energy and Protein Intake*

Both energy and protein are important in regulating IGF-I because each is essential for restoration of serum IGF-I concentrations after fasting. Refeeding a diet sufficient in calories and protein raises IGF-I to nearly 70% of the basal prefast values within 5 d, whereas refeeding a protein-deficient isocaloric diet results in a 2-d delay in the upward inflection of IGF-I and increases IGF-I to only 50% of control prefast values. In contrast, refeeding a diet deficient in both protein and energy results in a further decrease of IGF-I in serum *(8)*. The importance of energy intake in regulating IGF-I is supported by the observation that there is a threshold energy requirement (similar or equal to 11 kcal/kg/d) below which optimal protein intake fails to raise IGF-I during fasting *(9)*. The source of energy also might be critical for the regulation of serum IGF-I because the carbohydrate content of the diet appears to be a major determinant of the response of IGF-I to GH when energy intake is severely restricted *(10)*. The role of protein intake in the regulation of IGF-I is illustrated by the observation that the increase in IGF-I after fasting is proportional to the protein content of the refeeding diet. The quality of dietary protein is also important because IGF-I concentrations after fasting

are restored more readily by a protein-restricted diet rich in essential amino acids than by one that is rich in nonessential amino acids *(11)*.

Energy and amino acid deprivation do not appear to play a major role in the decline of IGF-I observed in critically ill patients. Evidence obtained mainly from animal models suggests that factors, such as cytokines, glucocorticoids, and acidosis, are important in this regard.

## 3. MECHANISMS INVOLVED IN THE NUTRITIONAL REGULATION OF IGF-I PRODUCTION

### *3.1. Role of GH Secretion*

Because GH is the principal hormonal stimulus of IGF-I production, impaired GH secretion may cause decreased IGF-I concentrations when food intake decreases (Fig. 1). In rats, the pulsatile secretion of GH is markedly attenuated by decreased availability of nutrients *(12)*, and this could result in the decline of serum IGF-I. Unlike rats, however, humans *(13)* and other species have increased GH secretion when food intake is decreased. Fasting for 5 d increases the 24-h integrated GH concentration and the maximum amplitude and pulse frequency of GH *(13)*. These observations suggest that impaired GH secretion is not responsible for decreased serum IGF-I concentrations in food-restricted humans.

Decreased GH secretion in starved rats could result from increased somatostatin, somatotropin-releasing inhibitory hormone (SRIH), tone or from reduced growth hormone-releasing hormone (GHRH) stimulation of somatotroph cells *(14)*. The involvement of SRIH is suggested by in vivo immunoneutralization studies in which GH secretion is restored in fasted rats after intravenous injection of antiserum to SRIH *(15)*. Increased SRIH observed in the peripheral circulation of fasted rats likely originates more probably from peripheral sources (gastrointestinal tract and pancreas) and not the hypothalamus *(12,16,17)*. These observations suggest that a relative or absolute excess of SRIH is involved in fasting-induced inhibition of GH secretion. The decline in GH secretion during fasting could also result from diminished GHRH secretion because levels of GHRH mRNA in the hypothalamus are decreased markedly after 72 h of fasting *(16)*. This decrease, however, is not associated with a reduction in hypothalamic GHRH peptide content, suggesting that release of peptide may be decreased in parallel with the reduction in mRNA. Given the evidence for an inhibitory effect of SRIH on GHRH release *(18)*, the imbalance between GHRH mRNA and peptide in the hypothalamus might be secondary to high SRIH tone. Lack of dietary protein blunts spontaneous GH secretion *(19)*. The protein content of the diet seems to be critical for the regulation of hypothalamic GHRH gene expression *(20)*. Furthermore, dietary protein restriction attenuates GH responsiveness to GHRH and reduces pituitary size and GH content.

Several extrahypothalamic hormones are also implicated in the regulation of GH secretion and might be involved in nutrition-induced alterations in GH secretion. Leptin, a product of adipose tissue, is capable of entering the brain to inhibit food intake and increase energy expenditure. Because administration of leptin antiserum to rats causes a marked decrease in GH secretion *(21)* and leptin levels are reduced by fasting in rats as in humans *(22–24)*, it has been suggested that leptin may be an integrative

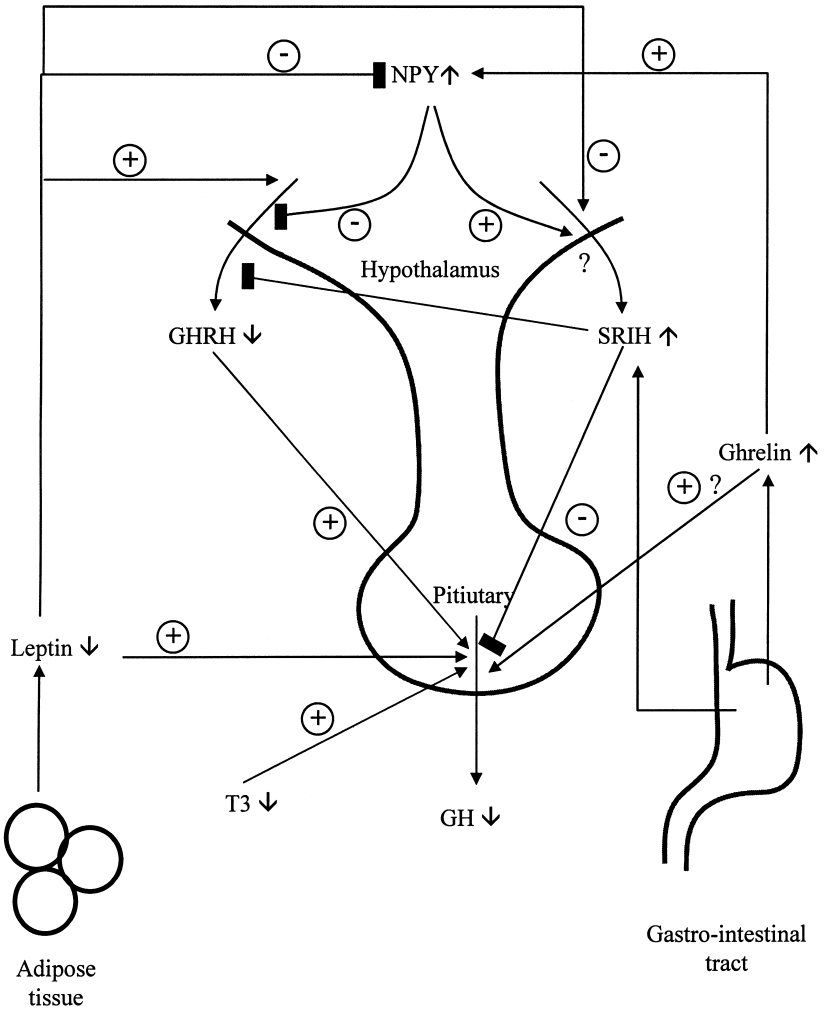



**Fig. 1.** Regulation of GH secretion by fasting in the rat. GH, growth hormone; SRIH, somatotropin-releasing inhibitory hormone; GHRH, growth hormone-releasing hormone; NPY, neuropeptide Y; T3, triiodothyronine.

signal for coordinating growth with nutritional status. This is supported by the observation that exogenous leptin prevents the fasting-induced fall of serum GH in rats *(25–27)*. Despite its stimulatory effect on GH secretion, exogenous leptin does not restore serum IGF-I in fasted animals to normal. The effect of leptin on GH secretion in rats appears to be exerted at the hypothalamic level by regulating neurons that produce GHRH, SRIH, and neuropeptide Y (NPY). The rescue of GH secretion by leptin may be mediated by preventing decline of GHRH mRNA, and induction of NPY mRNA in fasted rats *(26)*. Alternatively, the GH-releasing activity of leptin may be mediated in part by inhibition of SRIH *(28)*, as suggested by the ability of leptin to decrease SRIH mRNA and secretion in vitro *(29)*. Finally, leptin may stimulate GH secretion directly,

as illustrated by in vitro experiments *(30)*. The effects of leptin on GH secretion in humans remain to be clarified.

Ghrelin, an important regulator of GH secretion and energy homeostasis *(31)* produced mainly by the stomach, is regulated by nutrient intake *(32)* and promotes GH release at both the hypothalamic and pituitary levels *(33)*. Although both GH and ghrelin increase during fasting in humans, no correlations seem to exist between plasma ghrelin and GH or IGF-I concentrations. Further investigation is needed to delineate the role of ghrelin in enhancing GH secretion in fasting humans. Thyroid hormones stimulate the production of growth hormone in cultures of GH1 pituitary cells *(34)*, and decreased plasma triiodothyronine (T3) in fasted rats has been implicated in the decrease of GH mRNA in the pituitary during fasting *(35)*. Moreover, retinoic acid, acting in synergy with thyroid hormones, stimulates production of growth hormone in cultured pituitary cells *(36,37)*. We speculate that the stunted growth accompanying vitamin A deficiency might be mediated by decreased GH production.

GH secretion of rats is impaired in several other models of dietary manipulation that are accompanied by growth retardation and low serum IGF-I concentrations (lysine deficiency, potassium deficiency, zinc deficiency and selenium excess) as well as in response to stressful stimuli such as sepsis *(38)*.

### *3.2. Role of GH Receptor and Postreceptor Defects*

It is unlikely that impaired GH secretion alone causes the decrease in IGF-I observed in nutritionally restricted rats because the administration of GH to fasted or protein-restricted rats does not produce a normal increase of IGF-I in blood *(39–43)*. Also, protein energy malnutrition in humans is accompanied by high circulating concentrations of GH that fail to maintain IGF-I in the normal range *(44,45)*. These observations suggest that GH resistance accompanies nutritional deprivation. Because the liver is a principal site for production of IGF-I *(46,47)*, reduction of GH binding by the liver could impair production of IGF-I. Rats that are fasted exhibit parallel decline in serum IGF-I concentrations and in somatogenic (GH) binding capacity in liver *(48)*.

Changes in hepatic GH receptors (GHR) caused by dietary restriction of rats are paralleled by changes in concentrations of GH binding protein (GHBP) in serum *(49)*. In humans, GHBP decreases in parallel with serum IGF-I concentrations during severe dietary restriction *(50)*. However, the consequences of changes in circulating GHBP in the control of GH action are disputed.

Regulation of the GHR by fasting occurs at the level of gene expression *(51)*. GH receptor mRNA is reduced by fasting *(52,53)*, and the magnitude and time-course of this decline is similar to the decline in liver IGF-I mRNA, suggesting that there may be a causal relationship between the two. This decline in GHR mRNA may be driven in part by nutritionally induced changes in hormones, such as glucocorticoids, thyroid hormones, and insulin, or in metabolites such as glucose. Glucocorticoids in excess *(54,55)*, insufficient thyroid hormones *(56–58)* or insulin *(59–61)*, and reduced supply of glucose *(62,63)* that occur in response to food deprivation are associated with low liver GHR binding and mRNA. Decreased liver GHR mRNA occurs in humans who have GH resistance caused by malnutrition *(64)* or postoperative catabolism *(65)*. GH resistance associated with decreased liver GHR mRNA and binding is also present in

**Table 1**
**Effect of Fasting, Sepsis, and Chronic Renal Failure on GH-Induced JAK-2, GHR, STAT-5 Phosphorylation, and on SOCS-3 Gene Expression**

| | *Fasting* | *Sepsis* | *Chronic renal failure* |
|---|---|---|---|
| P-JAK-2/JAK-2 | ↘ | ↘ | ↘ |
| P-GHR/GHR | ↘ | ND | ND |
| P-STAT-5/STAT-5 | ↘ | ↘ | ↘ |
| SOCS-3 mRNA | ↗↗ | ↗↗ | ↗↗ |

P, phosphorylated; JAK, Janus kinase; STAT, signal transducers and activators of transcription; SOCS, suppressors of cytokine signaling; GHR, growth hormone receptor; ND, not determined.

other dietary models of malnutrition, such as zinc deficiency *(66)* and in catabolic conditions, such as chronic renal failure *(67)* and sepsis *(68)*.

In contrast to fasting, the role of the liver GH receptors in the decline of serum IGF-I in protein restriction is more questionable. Although protein restriction in young rats results in a dramatic decline of serum IGF-I, liver GH binding sites decrease only modestly. In older animals, protein restriction also causes a decline in serum IGF-I but does not reduce GH binding to liver membranes *(69)* or to freshly isolated hepatocytes *(70)*. Also, no changes in serum GHBP are observed *(71)*. Serum IGF-I responses to a single injection of GH in hypophysectomized protein-restricted animals are severely blunted *(42)*. Despite the fact that continuous infusion of GH into protein-restricted rats increases liver GH binding to the level of control-fed rats, serum IGF-I is not increased *(43)*. Taken together, these studies suggest that a postreceptor defect in GH action may participate in the GH resistance observed in protein restriction.

Intracellular defects in GH action could be a direct effect of limited nutrients or could result from secondary hormonal changes. Although it is not clear whether this postreceptor defect is specific to GH or is one that limits the synthesis of IGF-I regardless of the stimulus, the latter alternative seems the more likely. In hepatocyte primary cultures, the stimulation of IGF-I gene expression by insulin *(72)* as well as by GH *(73)* is blunted by a reduction in the concentration of amino acids in the medium.

### *3.3. Role of GH Transduction Pathways*

Although the decrease in liver GH binding associated with fasting is well established, the consequences of this decline on the GH transduction pathway are less clear (Table 1). To investigate the effect of fasting on the liver GH transduction pathway, Beauloye et al. assessed the activation of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway in response to GH injected in the portal vein of fasted and fed rats *(74)*. Although GH stimulated the phosphorylation of JAK-2, GHR, and STAT-5 in fed animals, the phosphorylation of these molecules was blunted markedly in the fasted animals. The inhibitory effect of fasting on these GH signaling molecules occurred without any changes in their protein content. The effect of fasting on GH-induced GHR and STAT-5 phosphorylation was detectable as early as 3 min after GH treatment and persisted at least until 30 min after GH injection. These findings suggest that the effects of fasting on the GHR signaling pathway are not caused by

delayed GH activation. The observation that the phosphorylation of STAT-5 by JAK-2 is required for GH to stimulate IGF-I expression *(75)* supports the role of the alterations caused by fasting in the decrease of liver IGF-I production.

Although the mechanisms by which fasting alters the JAK-STAT pathway remains to be determined, it is likely that this defect results mainly from decreased liver GH binding sites. Another mechanism might be the superinduction of an intracellular negative feedback loop mediated by suppressors of cytokine signaling (SOCS) proteins. The ability of overexpressed SOCS-3 to blunt JAK-STAT activation in transfected cells *(76,77)* and the increased SOCS-3 expression by fasting *(74)* suggest a role for SOCS-3 in the fasting-induced JAK-STAT alterations. Impaired JAK-STAT signal transduction, possibly mediated through decreased GH receptors and SOCS proteins overexpression, may also contribute to the GH resistance observed in chronic renal failure *(78)* and in sepsis *(79)*.

## *3.4. Role of Hormones in the Nutritional Regulation of IGF-I*

### 3.4.1. Insulin

Dietary restriction causes serum insulin concentrations to decline. Insulin-deficient diabetic rats have low serum IGF-I and decreased liver GH binding *(60,80,81)*. Replacement of insulin restores both to normal. Insulin, therefore, might regulate serum IGF-I concentrations through changes in liver GH binding *(82)*. The addition of insulin to hepatocytes in culture increases GHR mRNA and GH binding *(61,83)*. Recent onset or mild streptozotocin-induced diabetes in rats, however, can be accompanied by low serum IGF-I without change in hepatic GH binding *(84)*. In this situation, the decline of IGF-I is attributed to a postreceptor defect, likely related to the insulin deficiency directly, or less likely to metabolic abnormalities caused by insulin deficiency. In primary cultures of hepatocytes, insulin stimulates the accumulation of IGF-I mRNA in the absence of GH *(85,86)*. Insulin also potentiates the stimulatory effect of GH and amino acids on IGF-I production *(72,85,87)*. Although its exact mechanism of action is not known, the stimulatory effect of insulin seems to result from an enhanced rate of IGF-I gene transcription (Fig. 2) in adult hepatocytes *(88)* and from enhanced IGF-I mRNA stability in fetal hepatocytes *(89)*. Despite insulin's stimulatory role on IGF-I production, protein restriction (and perhaps decreased availability of specific amino acids) may be more important mechanistically than decline in serum insulin concentrations for the decreased circulating IGF-I in protein-restricted rats *(90)*. In rats made diabetic with streptozotocin who are treated with insulin and then submitted to a low- or normal protein diet, the diet decline in IGF-I persists despite high circulating insulin (two to three times normal values). This suggests that dietary protein restriction decreases serum IGF-I independent of insulin and that protein restriction by itself is the major cause of reduced serum IGF-I in this model.

### 3.4.2. Thyroid Hormones

The involvement of the thyroid hormones in the nutritional regulation of IGF-I is suggested by the close relationship between the decline of circulating IGF-I and of thyroxine (T3) in fasted humans *(91)* and rats *(92)*. Low serum IGF-I in hypothyroid animals reinforces the possibility of thyroid hormone regulation of IGF-I *(93)*. It is possible, however, that the major effect of thyroid hormones on IGF-I synthesis is

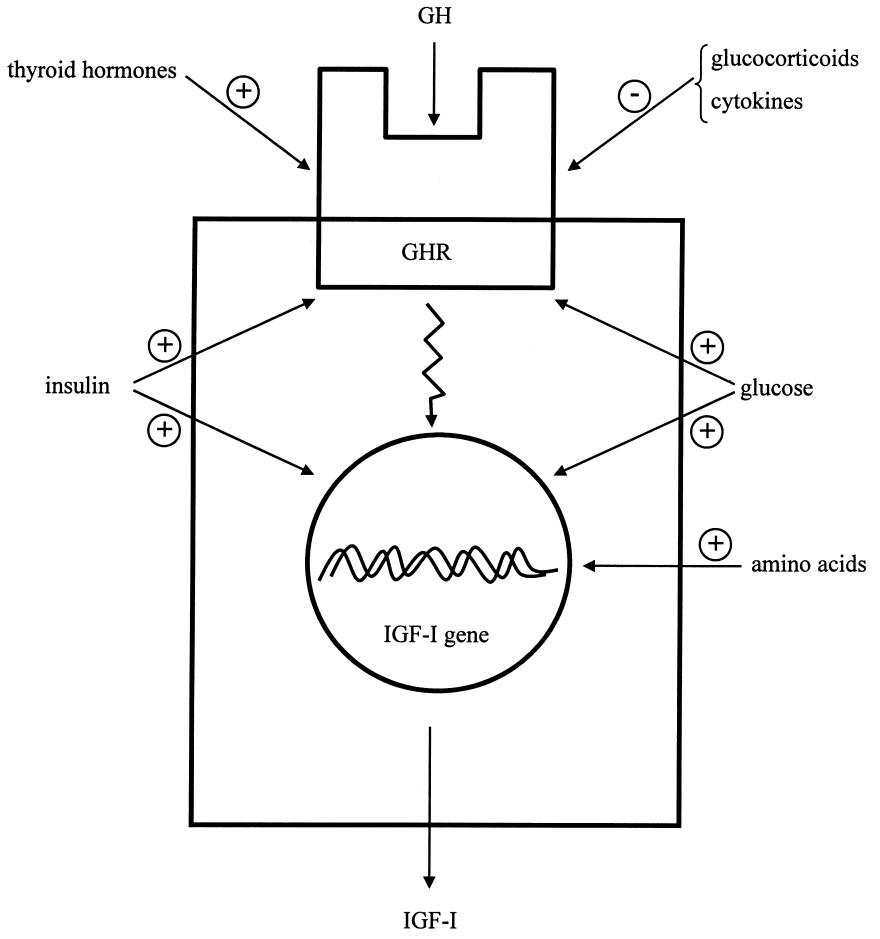



**Fig. 2.** Role of hormonal changes and nutrient availability in the regulation of IGF-I production by liver in response to food deprivation. GH, growth hormone; GHR, growth hormone receptor.

exerted on the pituitary *(94)*, where thyroid hormones regulate GH gene expression *(95)*. Hypothyroidism is not only accompanied by a decline in GH secretion but is also associated with blunted IGF-I production in response to GH and resistance to the growth-promoting effect of GH *(93)*. This suggests that thyroid hormones participate in IGF-I production by the liver. Studies show that thyroid hormones potentiate hepatic IGF-I synthesis in response to GH both in vivo and in vitro *(83,96)*. Hepatic GH binding is upregulated by thyroid hormones. This supports the role of thyroid hormones in the potentiation of GH induction of IGF-I. Low serum T3 concentrations might play a role in the decline in GH and serum IGF-I concentrations in fasted rats because treatment of fasted rats with T3 seems to attenuate the decline in serum IGF-I *(97)*.

### 3.4.3. Glucocorticoids and Proinflammatory Cytokines

A role for glucocorticoids in the GH resistance caused by food deprivation is suggested by their inhibitory effect on GH-induced IGF-I production in vivo *(98)* and in

vitro *(55,99)* concurrent with their increased circulating concentrations during fasting. Part of the GH resistance caused by excess glucocorticoids might be caused by their capacity to inhibit GHR mRNA and GH binding to hepatocytes *(54,55)* and to other cell types *(99,100)*. In diabetic rats, which have increased glucocorticoids and GH resistance, adrenalectomy restores the GH-induced IGF-I response *(101,102)*. In contrast with diabetic rats, however, adrenalectomy of fasted animals failed to reverse the fasting-induced inhibition of the early steps of the liver GH receptor-signaling pathway *(74)*. In addition to inhibit IGF-I production, glucocorticoids may also impair growth by induction of IGFBP-1 and reduction of free IGF-I *(103)* in the circulation.

In severe catabolic states such as sepsis, proinflammatory cytokines, namely tumor necrosis factor-α, interleukin-1β, and interleukin-6 are implicated in the development of GH resistance and the decrease in circulating IGF-I (refs. *104–106*; see also chapter 16). As reviewed in Chapter 3, metabolic acidosis, as in renal failure, also has been shown to cause resistance to GH *(107)* and to decrease circulating IGF-I *(108)*.

### *3.5. The Role of Nutrient Availability in the Nutritional Regulation of IGF-I*

Evidence for a direct role of amino acid availability in regulating IGF-I comes from experiments using primary cultures of rat hepatocytes *(109)*. In this model, amino acid deprivation causes a rapid and progressive decline in IGF-I mRNA and IGF-I peptide production, whereas amino acid excess causes an increase *(73,88)*. Among the amino acids, tryptophan seems to be the most critical in regulating IGF-I, as its removal from the medium for 48h causes a dramatic decline in IGF-I mRNA and in IGF-I release. Across a broad range of amino acid concentrations, GH and insulin raised IGF-I mRNA levels in proportion to the amino acid concentration *(110)*. Taken together, these observations suggest that GH, insulin and amino acids can regulate hepatic production of IGF-I independently.

It is not known, however, whether amino acids, insulin and GH control IGF-I synthesis at the same point. Whereas insulin and GH are believed to act at the transcriptional level, decreased IGF-I mRNA in amino acid-deprived cultured hepatocytes results from decreased transcription rate *(88)* and enhanced degradation *(111)*. An amino-responsive element has been described in the IGF-I gene *(112)*. It does not seem, however, to share common features with the one characterized in the *CHOP* and *asparagine synthase* genes, two genes induced by amino acid deprivation *(113)*. Several transcription factors appear to be affected by dietary protein/amino acid availability, but it remains to be determined whether these are involved in the observed effects of amino acids on IGF-I transcription. Restriction of amino acids leads to accumulation of uncharged transfer RNA, which could impair gene expression by altering the rate of transcription *(114)*.

In parallel with inhibition of IGF-I, amino acid deficiency stimulates the in vitro expression and release of IGFBP-1, a binding protein considered to inhibit the actions of IGF-I. Limitation in any one of the essential amino acids causes strong induction of IGFBP-1 *(73,115)*. However, restriction in vivo of single essential amino acids is not sufficient to induce IGFBP-1, and general amino acid depletion is necessary *(116)*. The direct effect of amino acid deprivation on IGFBP-1 explains why higher levels of IGFBP-1 are observed in protein-restricted rats than in starved rats.

IGF-I gene expression also may be regulated by glucose in hepatocytes, particularly those of fetal origin *(63,117)*. In this model, glucose stimulates IGF-I mRNA and pep-

tide secretion. Experiments with analogs suggest that glucose-6 phosphate is necessary for the induction of IGF-I mRNA. A similar observation was made for IGF-II. The glucose-induced rise in IGF-II mRNA was mediated by stimulation of gene transcription and increased transcript stability. This effect was observed in the absence of GH, indicating that it did not result from the potentiation of the GH action on IGF-I *(63)*.

Although reduced amino acid availability is thought to be responsible for the decrease of liver IGF-I mRNA in response to protein restriction, such a direct mechanism does not seem to be the rule for all nutrients. For example, chelation-induced depletion of zinc in rat hepatocytes does not cause IGF-I gene expression to decline, despite the clear inhibition of the metallothionein mRNA *(118)*.

### *3.6. Role of Changes in IGF-I Gene Expression*

Decreased serum IGF-I in dietary energy or protein restriction correlates with reduced steady-state levels of hepatic IGF-I mRNA *(119–122)*, suggesting that nutritional regulation of IGF-I gene expression takes place at a pretranslational level. In fasted animals, the levels of IGF-I mRNAs with different 5′ untranslated regions (class 1 and class 2 transcripts) appear to be coordinately decreased *(123,124)*. However, although the levels of IGF-IB mRNA declined markedly, IGF-IA mRNA was not altered significantly *(125)*. Despite this preferential decrease in IGF-IB mRNA, fasting caused both propeptides IGF-IA and IGF-IB to decrease *(123,125)*. All size-class transcripts (0.8–1.2, 1.7, 4.7, and 7.5 kb) are proportionately reduced by fasting *(53)*. Dietary protein restriction, however, caused a greater decrease of the 7.5 kb IGF-I mRNA than the other size-classes *(122,126)*.

Based on nuclear run-off studies *(53,111,125)* and analysis of nuclear transcripts *(127,128)*, both transcriptional and posttranscriptional mechanisms may mediate the decrease in IGF-I expression observed in fasted as well as protein-restricted animals.

The weight of evidence suggests that transcription is the major locus for nutritional regulation of IGF-I. The co-ordinate decrease in transcription of nutritionally sensitive genes, such as albumin, transthyretin, and IGF-I in protein-restricted rats might result from altered activity of transcription factors. The DNA binding activity of factors involved in the expression of the IGF-I gene in liver (hepatocyte nuclear factor [HNF]-1α, HNF-3, HNF-4, CCAAT/enhancer binding protein [C/EBP], Sp1) is altered in response to protein restriction *(129)*. The transcriptional activity of HNF-1α is reduced in hepatocytes exposed to medium deficient in amino acids *(130)*. In contrast, C/EBP homologous protein (the CHOP transcription factor) is stimulated in these conditions *(131,132)*. The induction of CHOP is of interest as increased levels of CHOP could interfere with C/EBP binding *(133)*. Although the role of HNF-1α and C/EBPα in the stimulation of basal expression of IGF-I in liver is well established *(134,135)*, their contribution to reduced IGF-I gene expression in the liver of protein-restricted rats is unsettled. Other transcription factors involved in the transcriptional regulation of IGF-I, such as Sp1 *(136)*, might also direct the response to nutrient availability *(137)*.

Nutritional regulation also seems to take place at the nuclear RNA splicing step. The observation that IGF-IA and IGF-IB mRNAs result from alternative splicing after transcription of a single gene, yet only IGF-IB mRNA levels are decreased by fasting suggests that the decrease in liver total IGF-I mRNA might also involve regulation of the pre-mRNA processing *(111)*.

Protein restriction may result in decreased stability of the IGF-I mRNA, in particular for the 7.5-kb transcript *(122,126)*. Reduction of the 7.5-kb transcript in protein restricted rats is confirmed by the observation that IGF-I mRNA stability in vitro is decreased in hepatocytes exposed to amino acid deprivation *(111)*. In this model, the 7.5-kb mRNA is degraded faster than the two smaller IGF-I mRNA species. Differential regulation of the 7.5-kb IGF-I mRNA might be related to its 3′-untranslated region, which contains several AU-rich sequences *(138)*. Such sequences in other genes are known to interact with cytosolic RNA-binding proteins and to be involved in the regulation of the stability and/or translation of the mRNA *(139)*.

Regulation of IGF-I synthesis by nutrients also may be under translational control because discrepancies have been observed between serum IGF-I peptide concentrations and liver IGF-I mRNA levels *(122,140–142)*. In protein-restricted rats, injections of high doses of GH for 1 wk restores liver IGF-I mRNA abundance to normal without normalization of liver or serum IGF-I concentrations *(122)*. This divergent response to GH is not the result of a secretory defect of IGF-I because there was no accumulation of IGF-I in liver. It also seems unlikely that tissues other than liver might make significant contributions to the IGF-I released into the serum, given the observation that 80–90% of circulating IGF-I is produced by the liver *(47)*. The mechanisms responsible for this presumed impairment of the translation of IGF-I mRNA are not known. It appears, however, that all IGF-I mRNA size-classes are associated with polysomes, even in the liver of protein-restricted rats *(143)*, suggesting that they have the capacity to engage in IGF-I synthesis.

In addition to liver, reduced IGF-I mRNA during diet restriction is observed in most other organs *(52,123)*. The decrement in IGF-I gene expression, however, is most dramatic in the liver. Fasting of young rats for 48 h decreases IGF-I mRNA levels by 80% in liver and lung, by 60% in kidney and muscle, and by only 30% in stomach, brain, and testes. No changes are observed in the heart. In a different study, prolongation of fasting for 3 d caused IGF-I mRNA in heart muscle to decrease but caused no change in the brain *(52)*. Protein restriction for 1 wk, however, does not seem to reduce IGF-I mRNA in tissues (kidney, heart, diaphragm, brain, and aorta) other than liver *(52)* and muscle *(144)*. The decline of circulating IGF-I in mice in whom the ability of liver to produce IGF-I has been knocked out indicates that the decline of circulating IGF-I during protein restriction originates from nonhepatic as well *(145)*.

## 4. MECHANISMS INVOLVED IN THE NUTRITIONAL REGULATION OF IGF-I ACTION

### *4.1. Role of IGF Binding Proteins*

Among the proposed functions of the IGF binding proteins (IGFBPs) are the prolongation of the plasma half-life of IGF-I and IGF-II, control of the rate of IGF transport from the vascular compartment, and regulation of the interaction between IGF-I and the type 1 IGF receptor on the cell surface *(146–148)*. Because they control the bioavailability of IGF-I to tissues *(149)*, the IGFBPs are believed to exert both stimulatory *(150–152)* and inhibitory *(153–155)* effects on IGF-I actions (Table 2). IGF-I bioavailability may be controlled by posttranslational modifications of IGFBPs (partial proteolytic degradation by specific IGFBP proteases, selective dephosphorylation)

**Table 2**
**Effect of Food Deprivation on Circulating IGF-I and IGFBP Levels and Their Hepatic Gene Expression**

| | *Circulating levels* | *Hepatic gene expression* |
|---|---|---|
| IGF-I | Total ↙ | ↙ |
| | Free ↙ | |
| IGFBP-1 | ↗ | ↗ |
| IGFBP-2 | ↗ | ↗ |
| IGFBP-3 | ↘ | ↘ |
| ALS | ↘ | ~ |
| IGFBP-4 | ~ | ~ |

IGFBP, insulin-like growth factor binding protein; ALS, acid-labile subunit.

resulting in IGFBPs with reduced affinity for IGF-I. Less than 1% of IGF-I circulates as free peptide *(156)*, and most (>90%) is bound to the 150-kDa complex, which consists of IGF-I, IGFBP-3, or IGFBP-5 and an acid labile subunit (ALS). This complex is believed not to cross the capillary endothelium *(157)* and is credited with prolonging the half-life of IGF-I in the circulation. The complex has a relatively long half-life of 3–6 h in rats *(158)* and 12–15 h in humans *(159)*, whereas free IGF-I disappears with an apparent half-life of 14 min *(160)*. IGFBP-3 probably serves as a storage pool for IGF-I. IGFBP-1, IGFBP-2, and IGFBP-4 are associated with IGF-I in smaller complexes (30–40 kDa) that can cross the capillary endothelium *(161)*. IGFBP-1 and IGFBP-2 contain RGD sequences (Arg-Gly-Asp) *(149)* that may allow attachment to cell surface integrin receptors. They may be involved in the delivery of IGF-I to tissues. Although serum concentrations of IGFBP-3 correlate positively with ALS and total IGF-I, IGFBP-1 and free IGF-I correlate inversely. It is hypothesized that IGFBP-1 is an important determinant of free IGF-I in vivo *(162,163)*. IGF-independent actions have been shown for IGFBP-1, -3, and -5 *(149)*. In particular, IGFBP-3 binds specifically and with high affinity to the cell surface of various cell types and inhibits monolayer cell growth, presumably by specific interaction with cell membrane proteins that function as IGFBP-3 receptors *(164)*. The functions and nutrition-related regulatory mechanisms of IGFBP-5, IGFBP-6, and IGFBP-related proteins (Mac25, CTGF, NOV, CYR61) *(165)* are largely unknown.

Nutrient intake is a major regulator of the plasma concentrations of the IGFBPs. Serum IGFBP-3 concentrations in humans are relatively constant throughout the day, and this is the likely mechanism for the stability of serum IGF-I concentrations *(166)*. In contrast, serum IGFBP-1 is markedly and rapidly suppressed by nutrient intake *(167,168)*. An effect mediated primarily by increased insulin *(169,170)*, glucose *(171,172)*, and probably by amino acid concentrations *(73,116)*. Insulin also may selectively stimulate the transport of IGFBP-1 to the extravascular space *(173)*, which might explain the rapidity of the insulin-induced fall in IGFBP-1. IGFBP-2 levels are more stable than IGFBP-1 and are not subject to postprandial changes *(174)*.

Dietary manipulations change the abundance of serum IGFBPs in humans and animals. In general, dietary restriction decreases serum IGFBP-3 and ALS concentrations

while it increases serum IGFBP-1 and IGFBP-2 *(5)*. Fasting of rats for 24 h increases serum IGFBP-1 and -2 *(175,176)*, and produces parallel increases of liver IGFBP-1 and IGFBP-2 mRNA *(177)*. Likewise, 24-h fasting in humans causes a 4-fold increase of IGFBP-1 *(162,168)* whereas prolonged fasting for 9 d or protein restriction for 6 d is needed to cause an increase in plasma IGFBP-2 *(174,178)*. Maternal fasting also induces an increase of IGFBP-1 and IGFBP-2 in fetal serum *(179)*, thereby increasing the IGF binding capacity of serum. Free IGF-I changes in parallel with total IGF-I in fasted rats *(180)* and children *(162)*. Unlike IGFBP-1, fasting for 24 h does not affect serum IGFBP-3 *(181)* and ALS *(180)* in rats and humans. A decline of serum IGFBP-3 and ALS, however, occurs after fasting for 48–72 h *(179,180,182)*.

During more chronic dietary restriction, serum IGFBP-3 declines and a parallel change in the liver IGFBP-3 mRNA is observed *(180,183)*. Unlike other situations in which IGFBP-3 concentrations are low, that is, pregnancy *(184)*, after surgery *(185)*, and catabolic states *(186)*, the decline of IGFBP-3 in food-deprived rats and humans is not associated with proteolytic activity in serum *(187)*. In response to reduced nutrition, serum ALS levels also decline, but steady-state hepatic ALS mRNA levels are not changed, indicating that ALS synthesis in fasting is regulated primarily at the posttranscriptional level *(180,188–190)*. Because both IGFBP-3 and ALS production is stimulated by GH and insulin *(188,191,192)*, it is not clear whether their decrease in response to food deprivation is due to decreased GH secretion, to defects in the GH action pathway and/or to the lack of the stimulatory effect of insulin. IGFBP-3 and ALS genes are stimulated directly by insulin, even in the absence of GH *(192)*. The decline of IGFBP-3 may be related to decreased serum IGF-I itself, because IGF-I infusion in protein-restricted-rats normalizes serum IGFBP-3 *(193)*. The induction of IGFBP-3 by IGF-I provides a mechanism by which the concentrations of these two peptides could be regulated coordinately. As with fasting, an increase in liver IGFBP-1 and -2 mRNA and increased serum concentrations of IGFBP-1 and -2 occurs with chronic energy or protein restriction *(71,183,189,190,194)*.

Changes in IGFBPs similar to those produced by food deprivation have been observed in response to catabolic states. The most dramatic changes are an increase in circulating IGFBP-1 levels and the presence of an IGFBP-3 proteolytic activity. Proteolytic activity that degrades IGFBP-3 specifically appears in the circulation after major surgery *(185)* and in severe catabolic states *(186)*. The decreased affinity for IGF-I caused by the enzymatic alteration of IGFBP-3 is associated with increased free IGF-I *(195)*. This might increase the bioavailability of IGF-I for the tissues. Increases in IGFBP-2 and IGFBP-4 and decline in ALS levels are also observed *(186,196,197)*.

As a consequence of these changes, when the IGF binding by serum is evaluated by chromatography after the serum sample has been incubated with radiolabeled IGF-I, dietary restriction consistently causes a decrease in the 150-kDa complex and an increase in the small binding protein complex *(198,199)*. These changes might alter the transport of IGF-I across the endothelium and the bioavailability of IGF-I to the tissues.

### *4.2. Role of the Clearance of Circulating IGF-I*

Because IGFBPs are responsible for transport of IGF-I in the circulation, nutrient-induced changes in the concentrations of the IGFBPs could alter the clearance of circulating IGF-I. Plasma IGF-I clearance is accelerated in situations where serum IGFBP-3

is decreased, for example, hypophysectomized *(200)* or pregnant rats *(184)*. By monitoring the decline of radioactivity in the circulation of rats injected with [$^{125}$I]-IGF-I, it has been shown that the clearance and the volume of distribution of [$^{125}$I]-IGF-I were increased in protein-restricted rats by 50% and 75%, respectively *(199)*. Pharmacokinetic analysis indicates that the accelerated clearance of IGF-I in protein-restricted rats is the result of more rapid distribution of IGF-I into tissues (shorter $t_{1/2}$) rather than a change in the elimination half-life ($t_{1/2}$). In fed rats, IGF-I is almost equally distributed between the 150-kDa and the 30-kDa binding protein complexes, whereas in protein-restricted rats, IGF-I is bound preferentially to IGFBPs in the 30-kDa complex *(199)*. Because the small IGFBP complexes are believed to facilitate the transport of IGF-I from serum to tissues, the preferential association of IGF-I with these IGFBPs in protein-restricted animals might allow faster transcapillary passage and distribution to tissues. Unlike the rat, clearance of radiolabeled IGF-I in fasted sheep is not enhanced. This could result from species differences, or it could indicate that only chronic or a more specific dietary restriction affect clearance and distribution of IGF-I. Despite the rapid decline in circulating IGF-I after LPS injection, pharmacokinetic analysis of blood [$^{125}$I]-IGF-I decay curves indicates that the half-time for whole blood clearance is not altered by LPS *(201)*.

### *4.3. Role of the Sensitivity to IGF-I*

In addition to decreasing IGF-I production, dietary restriction impairs the anabolic actions of IGF-I. When protein restricted or zinc-deficient rats were infused with IGF-I by osmotic minipump, carcass growth (body weight and tibial epiphyseal plate) was not stimulated, despite the normalization of serum IGF-I *(193,202)*. In contrast, growth of the spleen and kidney was enhanced. Similarly, IGF-I failed to increase cancellous and periosteal bone formation in protein-restricted rats, while exogenous IGF-I increased the bone formation rate in well-fed rats *(203)*. In rats fed parenterally with a limited supply of amino acids, anabolic effects of IGF-I on carcass lean mass were not observed, in contrast to visceral tissues *(204)*. Treatment of neonatal protein energy-deprived rats with IGF-I does not stimulate somatic growth. In contrast, erythroid precursors in bone marrow are increased, suggesting that the actions of IGF-I on growth and erythropoiesis are unrelated *(205)*. These results suggest that, in addition to its effects on IGF-I gene expression and IGF binding proteins, food deprivation causes organ-specific resistance to the anabolic properties of exogenous IGF-I. These observations support the concept that nutrient insufficiency can block the anabolic properties of IGF-I, but do not block other properties *(206–208)*.

Resistance to IGF-I during food deprivation occurs despite increased binding of IGF-I by tissues. Rats that are fasted for 48 h have increased IGF-I binding to stomach, lung, testes, and kidney, as reflected by alterations in the IGF-I receptor number and/or affinity *(123)*. Change in the abundance of the type 1 IGF receptor mRNA parallels the change in binding. Protein restriction also is associated with an increase of IGF-I binding to muscle *(209)*.

That nutrients can control the response to IGF-I directly has been observed in fibroblast cultures where zinc depletion inhibits the mitogenic action of IGF-I *(210)*. Although the interaction between anabolic action of IGF-I and amino acid availability has not been studied at the cellular level, several pieces of evidence indicate that cross-

talk between the pathways activated by these stimuli are likely. For example, induction of the transcription factor CHOP by amino acid depletion requires the presence of IGF-I *(132)*. In muscle cells, a target for IGF-I action, amino acids activate p70 S6 kinase, an intermediate in the initiation of protein synthesis, in synergy with insulin *(211)*. Furthermore, both insulin and amino acids are required to stimulate protein synthesis and to inhibit protein degradation in muscle tissue *(212)*. If these observations can be extended to IGF-I, they suggest that amino acids might modulate the anabolic action of IGF-I, at least on protein metabolism.

The possibility that nutrients and hormones modulate the anabolic action of IGF-I has been investigated in humans. In energy restricted obese subjects, exogenous GH produced a twofold increase in serum IGF-I, accompanied by attenuation of nitrogen loss *(213)*. After a few weeks, however, resistance to the anabolic properties of IGF-I occurred. In similar experiments, infusion of IGF-I for 1 wk increased serum IGF-I concentrations fourfold and produced marked attenuation of the nitrogen wasting *(214)*. In volunteers made catabolic by glucocorticoid treatment, IGF-I infusion did not produce any significant decrease of proteolysis, suggesting that the anabolic action of IGF-I in humans may depend on the hormonal and nutritional environment *(215)*. GH administered together with IGF-I appears to function in a complementary fashion to promote protein anabolism *(216)*. There are several ways by which GH could produce nitrogen retention that are not fully replicated by infusion of IGF-I. For example, GH may alter concentrations of IGFBPs and modify the metabolism of carbohydrate or fat to facilitate IGF-I action.

The loss of anabolic response to IGF-I has been described in catabolic states, such as AIDS *(217)*, sepsis *(218)*, and uremia *(219)*. In uremia, resistance is caused by a postreceptor defect characterized by inhibition of the autophosphorylation of the type 1 IGF receptor (IGF-1R) β-subunit and IRS-1 *(220)*. Although perturbed IGFBPs in chronic renal failure may play an important role in altering IGF-I storage and delivery to tissues, IGF-I analogs with low affinity to IGFBPs fail to obliterate this IGF-I resistance *(220)*. In addition, malnutrition and acidosis have been excluded as mediators of the IGF-I resistance of uremic rats *(220)*. In more severe catabolic states, such as sepsis, the anticatabolic action of IGF-I can also be blunted. In rats made septic by cecal ligature and puncture, IGF-I failed to inhibit muscle proteolysis, despite the suppression of the gene expression of several components of the ubiquitin-proteasome proteolytic pathway *(221)*. However, IGF-I retained its antiproteolytic action in burned rats *(222)*. Careful dissection of the factors controlling the anabolic actions of IGF-I will need to be performed.

## 5. SUMMARY AND CONCLUSIONS

Nutrition is one of the principal regulators of circulating IGF-I.

- In humans, serum IGF-I concentrations are markedly reduced by energy and/or protein deprivation.
- Both energy and proteins are critical in the regulation of serum IGF-I concentrations. After fasting, optimal intake of both energy and protein is necessary for the restoration of circulating IGF-I, but energy may be somewhat more important than protein in this regard. While a low intake of protein is able to increase IGF-I in presence of adequate

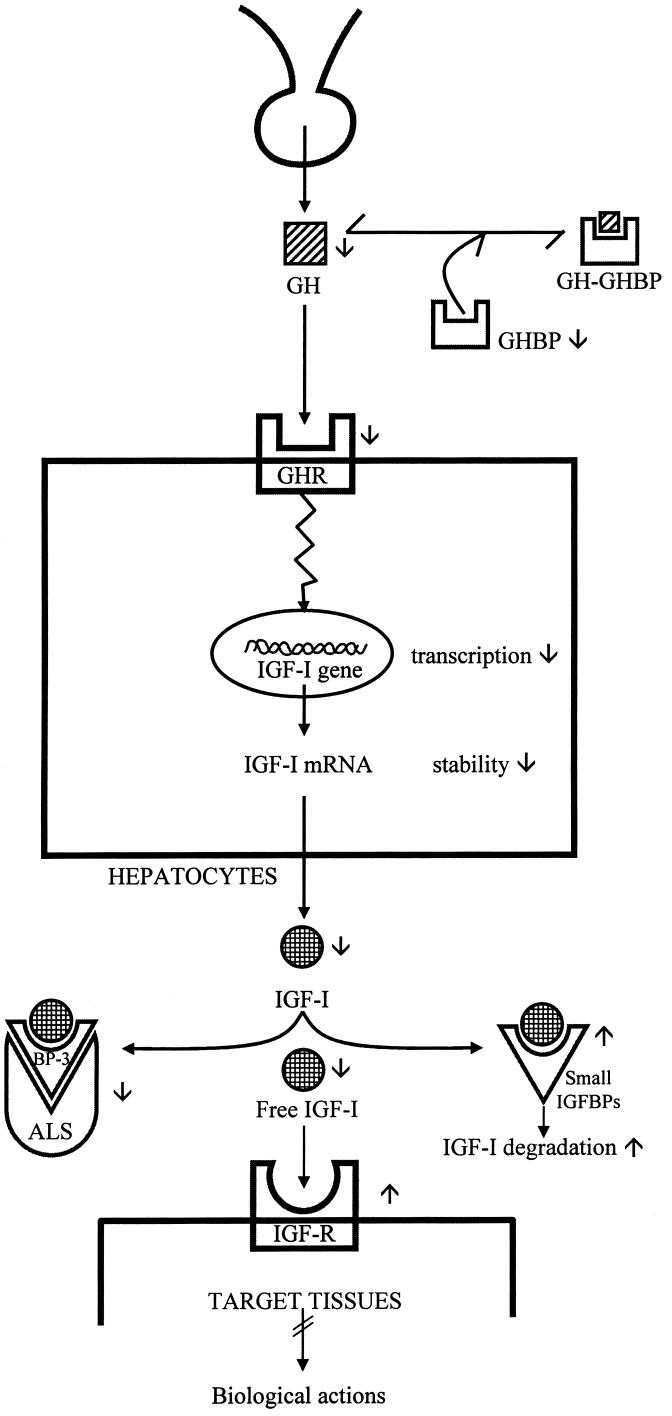



**Fig. 3.** Changes in IGF-I system induced by food deprivation. GH, growth hormone; GHBP, growth hormone binding protein; GHR, growth hormone receptor; ALS, acid-labile subunit; IGF-R, insulin-like growth factor receptors; IGFBP, IGF-binding proteins; BP-3, IGF-binding protein-3.

energy, there is a threshold requirement of energy below which optimal protein intake fails to raise IGF-I after fasting.
- When energy intake is severely reduced, the carbohydrate content of the diet is a major determinant of IGF-I responsiveness to GH.
- The content of essential amino acids in the diet is also critical for the optimal restoration of IGF-I after fasting.

Many mechanisms are involved in the nutritional regulation of IGF-I (Fig. 3).

- Decline of serum IGF-I during dietary restriction is independent of the diet-induced alterations in pituitary GH secretion.
- The role of liver GH receptors is dependent of the severity of the nutritional insult. In severe dietary restriction (fasting), a marked decrease of the number of somatogenic receptors suggests that a receptor defect is involved in the decline of circulating IGF-I. In contrast, in less severe forms of dietary restriction (protein restriction), the decline of IGF-I results from a postreceptor defect in GH action at the hepatic level.
- Nutritional deprivation decreases hepatic IGF-I production by diminishing IGF-I gene expression.
- Decline in IGF-I gene expression results from both transcriptional and post-transcriptional mechanisms.
- Decline in IGF-I gene expression is mainly caused by nutrient deficiency, and less importantly by nutritionally induced changes in hormones (insulin, T3).
- Diet restriction also increases the clearance and degradation of serum IGF-I through changes in the levels of circulating insulin-like growth factor-binding proteins (IGFBPs).
- Finally, nutrients may also control the biological action of IGF-I, either directly or indirectly through changes in IGFBPs.

GH resistance with decreased IGF-I production is also present in situations characterized by catabolic stress.

- Proinflammatory cytokines and glucocorticoids probably mediate the decreased IGF-I production in these situations.
- The molecular mechanisms leading to the decline of IGF-I seem to be similar to those operational in food deprivation.
- As with nutrients, these hormonal factors can control the anabolic action of IGF-I, in particular on skeletal muscle.

## REFERENCES

1. Haymond MW, Mauras N. The rationale for the use of recombinant human growth hormone and insulin-like growth factor-I for catabolic conditions in humans. Horm Res 1996;46:202–207.
2. Frost RA, Fuhrer J, Steigbigel R, Mariuz P, Lang CH, Gelato MC. Wasting in the acquired immune deficiency syndrome is associated with multiple defects in the serum insulin-like growth factor system. Clin Endocrinol (Oxf ) 1996;44:501–514.
3. Clemmons DR, Klibanski A, Underwood LE, McArthur JW, Ridgway EC, Beitins IZ, et al. Reduction of plasma immunoreactive somatomedin-C during fasting in humans. J Clin Endocrinol Metab 1981;53:1247–1250.
4. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. Endocr Rev 1994;15:80–101.
5. Argente J, Caballo N, Barrios V, Munoz MT, Pozo J, Chowen JA, et al. Multiple endocrine abnormalities of the growth hormone and insulin-like growth factor axis in patients with anorexia nervosa: effect of short- and long-term weight recuperation. J Clin Endocrinol Metab 1997;82:2084–2092.

6. Chu LW, Lam KSL, Tam SCF, Hu WJHC, Hui SL, Chiu A, et al. A randomized controlled trial of low-dose recombinant human growth hormone in the treatment of malnourished elderly medical patients. J Clin Endocrinol Metab 2001;86:1913–1920.
7. Ross R, Miell J, Freeman E, Jones J, Matthews D, Prece M, et al. Critically ill patients have high basal growth hormone levels with attenuated oscillatory activity associated with low levels of insulin-like growth factor-I. Clin Endocrinol (Oxf ) 1991;35:47–54.
8. Isley WL, Underwood LE, Clemmons DR. Dietary components that regulate serum somatomedin-C concentrations in humans. J Clin Invest 1983;71:175–182.
9. Isley WL, Underwood LE, Clemmons DR. Changes in plasma somatomedin-C in reponse to ingestion of diets with variable protein and energy content. JPEN 1984;8:407–411.
10. Snyder DK, Clemmons DR, Underwood LE. Dietary carbohydrate content determines responsiveness to growth hormone in energy-restricted humans. J Clin Endocrinol Metab 1989;69:745–752.
11. Clemmons DR, Seek MM, Underwood LE. Supplemental essential aminoacids augment the somatomedin-C/insulin-like growth factor-I response to refeeding after fasting. Metabolism 1985;34:391–395.
12. Tannenbaum GS, Rorstad O, Brazeau P. Effects of prolonged food deprivation on the ultradian growth hormone rhythm and immunoreactive somatostatin tissue levels in the rat. Endocrinology 1979;104:1733–1738.
13. Ho KY, Veldhuis JD, Johnson ML, Furlanetto R, Evans WS, Alberti KGMM, et al. Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man. J Clin Invest 1988;81:968–975.
14. Tannenbaum GS, Ling N. The interrelationship of growth hormone (GH)-releasing factor and somatostatin in generation of the ultradian rhythm of GH secretion. Endocrinology 1984;115:1952–1957.
15. Tannenbaum GS, Epelbaum J, Colle E, Brazeau P, Martin JB. Antiserum to somatostatin reverses starvation-induced inhibition of growth hormone but not insulin secretion. Endocrinology 1978;102:1909–1914.
16. Bruno JF, Olchovsky D, White JD, Leidy JW, Song J, Berelowitz M. Influence of food deprivation in rat on hypothalamic expression of growth hormone-releasing factor and somatostatin. Endocrinology 1990;127:2111–2116.
17. Wu V, Sumii K, Tari A, Sumii M, Walsh JH. Regulation of rat antral gastrin and somatostatin gene expression during starvation and after refeeeding. Gastroenterology 1991;101:1552–1558.
18. Katakami H, Downs TR, Frohman LA. Inhibitory effect of hypothalamic medial preoptic area somatostatin on growth hormone-releasing factor in the rat. Endocrinology 1988;123:1103–1109.
19. Harel Z, Tannenbaum GS. Dietary protein restriction impairs both spontaneous and growth hormone-releasing factor-stimulated growth hormone release in the rat. Endocrinology 1993;133:1035–1043.
20. Bruno JF, Song J, Berelowitz M. Regulation of rat hypothalamic preprogrowth hormone-releasing factor messenger ribonucleic acid by dietary protein. Endocrinology 1991;129:1226–1232.
21. Pombo M, Pombo CM, Astorga R, Cordido F , Popovic V, Garcia-Mayor RV, et al. Regulation of growth hormone secretion by signals produced by the adipose tissue. J Endocrinol Invest 1999;22(5 Suppl):22–26.
22. Palacio AC, Perez BF, Santos JL, Schlesinger L, Monckeberg F. Leptin levels and IgF-binding proteins in malnourished children: Effect of weight gain. Nutrition 2002;18:17–19.
23. Maccario M, Aimaretti G, Corneli G, Gauna C, Grottoli S, Bidlingmaier M et al. Short-term fasting abolishes the sex-related difference in GH and leptin secretion in humans. Am J Physiol Endocrinol Metab 2000;279:E411–E416.
24. Soliman AT, ElZalabany MM, Salama M, Ansari BM. Serum leptin concentrations during severe protein-energy malnutrition: correlation with growth parameters and endocrine function. Metabolism 2000;49:819–825.
25. Carro E, Se-aris R, Considine RV, Casanueva FF, Dieguez C. Regulation of in vivo growth hormone secretion by leptin. Endocrinology 1997;138:2203–2206.
26. Vuagnat BAM, Pierroz DD, Lalaoui M, Englaro P, Pralong FP, Blum WF, et al. Evidence for a leptin-neuropeptide Y axis for the regulation of growth hormone secretion in the rat. Neuroendocrinology 1998;67:291–300.
27. LaPaglia N, Steiner J, Kirsteins L, Emanuele M, Emanuele N. Leptin alters the response of the growth hormone releasing factor growth hormone insulin-like growth factor-I axis to fasting. J Endocrinol 1998;159:79–83.

28. Tannenbaum GS, Gurd W, Lapointe M. Leptin is a potent stimulator of spontaneous pulsatile growth hormone (GH) secretion and the GH response to GH-releasing hormone. Endocrinology 1998;139:3871–3875.
29. Quintela M, Senaris R, Heiman ML, Casanueva FF, Dieguez C. Leptin inhibits in vitro hypothalamic somatostatin secretion and somatostatin mRNA levels. Endocrinology 1997;138:5641–5644.
30. Baratta M, Saleri R, Mainardi GL, Valle D, Giustina A, Tamanini C. Leptin regulates GH gene expression and secretion and nitric oxide production in pig pituitary cells. Endocrinology 2002;143:551–557.
31. Horvath TL, Diano S, Sotonyi P, Heiman M, Tschöp M. Minireview: Ghrelin and the regulation of energy balance-A hypothalamic perspective. Endocrinology 2001;142:4163–4169.
32. Lee HM, Wang GY, Englander EW, Kojima M, Greeley GH, Jr. Ghrelin, a new gastrointestinal endocrine peptide that stimulates insulin secretion: enteric distribution, ontogeny, influence of endocrine, and dietary manipulations. Endocrinology 2002;143:185–190.
33. Kojima M, Hosoda H, Matsuo H, Kangawa K . Ghrelin: discovery of the natural endogenous ligand for the growth hormone secretagogue receptor. Trends in Endocrinology and Metabolism 2001;12:118–122.
34. Samuels HH, Horwitz ZD, Stanley F, Casanova J, Shapiro LE. Thyroid hormone controls glucocorticoid action in cultured GH1 cells. Nature 1977;268:254–257.
35. Yanagisawa M, Fukasawa N, Hase K, Sakurai S, Sakatsume Y, Iitaka M, et al. The effect of triiodothyronine replacement on the pituitary growth hormone gene expression in the fasting rat. 73th Endocrine Society Meeting abstract #202, 1991.
36. Bedo G, Santisteban P, Aranda A. Retinoic acid regulates growth hormone gene expression. Nature 1989;339:231–234.
37. Morita S, Fernandez-Mejia C, Melmed S. Retinoic acid selectively stimulates growth hormone secretion and messenger ribonucleic acid levels in rat pituitary cells. Endocrinology 1989;124:2052–2056.
38. Peisen JN, McDonnell KJ, Mulroney SE, Lumpkin MD. Endotoxin-induced suppression of the somatotropic axis is mediated by interleukin-1beta and corticotrophin-releasing factor in the juvenile rat. Endocrinology 1995;136:3378–3390.
39. Phillips LS, Young HS. Nutrition and somatomedin. I. Effect of fasting and refeeding on serum somatomedin activity and cartilage growth activity in rats. Endocrinology 1976;99:304–314.
40. Takano K, Hizuka N, Kawai K, Shizume K. Effect of growth hormone and nutrition on the level of somatomedin A in the rat. Acta Endocrinol (Copenh) 1978;87:485–494.
41. Shapiro B, Pimstone BL. Sulphation factor (somatomedin activity) in experimental protein malnutrition in the rat. J Endocrinol 1978;77:233–240.
42. Maes M, Amand Y, Underwood LE, Maiter D, Ketelslegers JM. Decreased serum insulin-like growth factor-I response to growth hormone in hypophysectomized rats fed a low protein diet: evidence for a postreceptor defect. Acta Endocrinol (Copenh) 1988;117:320–326.
43. Thissen JP, Triest S, Underwood LE, Maes M, Ketelslegers JM. Divergent responses of serum insulin-like growth factor-I and liver growth hormone (GH) receptors to exogenous GH in protein-restricted rats. Endocrinology 1990;126:908–913.
44. Grant DB, Hambley J, Becker D, Pimstone BL. Reduced sulphation factor in undernourished children. Arch Dis Child 1973;48:596–600.
45. Soliman AT, Hassan AEI, Aref MK, Hintz RL, Rosenfeld RG, Rogol AD. Serum Insulin-like growth factor I and II concentrations and growth hormone and insulin responses to arginine infusion in children with protein-energy malnutrition before and after nutritional rehabilitation. Pediatr Res 1986;20:1122–1130.
46. Schwander JC, Hauri C, Zapf J, Froesch ER. Synthesis and secretion of insulin-like growth factor and its binding protein by the perfused rat liver: dependence on growth hormone status. Endocrinology 1983;113:297–305.
47. Sjögren K, Liu JL, Blad K, Skrtic S, Vidal O, Wallenius V, et al. Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. Proc Natl Acad Sci USA 1999;96:7088–7092.
48. Maes M, Underwood LE, Ketelslegers JM. Plasma somatomedin-C in fasted and refed rats: close relationship with changes in liver somatogenic but not lactogenic binding sites. J Endocrinol 1983;97:243–252.
49. Mulumba N, Massa G, Ketelslegers JM, Maes M. Ontogeny and nutritional regulation of the serum growth hormone binding protein in the rat. Acta Endocrinol (Copenh) 1991;125:409–415.

50. Hochberg Z, Hertz P, Colin V, Ish-Shalom S, Yeshurun D, Youdim MBH et al. The distal axis of growth hormone (GH) in nutritional disorders: GH-binding protein, insulin-like growth factor-I (IGF-I), and IGF- I receptors in obesity and anorexia nervosa. Metabolism 1992;41:106–112.
51. Schwartzbauer G, Menon RK. Regulation of growth hormone receptor gene expression. Mol Genet Metab 1998;63:243–253.
52. Bornfeldt KE, Arnqvist HJ, Enberg B, Mathews LS, Norstedt G. Regulation of insulin-like growth factor-I and growth hormone receptor gene expression by diabetes and nutritional state in rat tissues. J Endocrinol 1989;122:651–656.
53. Straus DS, Takemoto CD. Effect of fasting on insulin-like growth factor-I and growth hormone receptor mRNA levels and IGF-I gene transcription in rat liver. Mol Endocrinol 1990;4:91–100.
54. Gabrielsson BG, Carmignac DF, Flavell DM, Robinson ICAF. Steroid regulation of growth hormone (GH) receptor and GH-binding protein messenger ribonucleic acids in the rat. Endocrinology 1995;136:209–217.
55. Beauloye V, Ketelslegers J-M, Moreau B, Thissen J-P. Dexamethasone inhibits both growth hormone (GH)-induction of insulin-like growth factor-I(IGF-I) mRNA and GH receptor (GHR) mRNA levels in rat primary cultured hepatocytes. Growth Hormone IGF Res 1999;9:205–211.
56. Dauncey MJ, Burton KA, White P, Harrison AP, Gilmour RS, Duchamp C et al. Nutritional regulation of growth hormone receptor gene expression. FASEB J 1994;8:81–88.
57. Romero GS, Stephan DA, Sperling MA, Menon RK. Distinct sexual dimorphism in the effect of hypothyroidism on the expression of the growth hormone receptor and growth hormone- binding protein gene in rat liver. Horm Res 1996;45:273–278.
58. Mullis PE, Eblé A, Marti U, Bürgi U, Postel-Vinay MC. Regulation of human growth hormone receptor gene transcription by triiodothyronine (T3). Mol Cell Endocrinol 1999;147:17–25.
59. Menon RK, Stephan DA, Rao RH, Shen-Orr Z, Downs LS, Jr., Roberts CT, Jr., et al. Tissue-specific regulation of the growth hormone receptor gene in streptozocin-induced diabetes in the rat. J Endocrinol 1994;142:453–462.
60. Maes M, Ketelslegers JM, Underwood LE. Low plasma somatomedin-C in streptozotocin-induced diabetes mellitus: correlation with changes in somatogenic and lactogenic liver binding sites. Diabetes 1983;32:1060–1069.
61. Leung KC, Doyle N, Ballesteros M, Waters MJ, Ho KKY. Insulin regulation of human hepatic growth hormone receptors: Divergent effects on biosynthesis and surface translocation. J Clin Endocrinol Metab 2000;85:4712–4720.
62. Niimi S, Hayakawa T, Tanaka A, Ichihara A. Glucose regulation of growth hormone receptors in primary cultured rat hepatocytes. Endocrinology 1991;129:2734–2739.
63. Brameld JM, Gilmour RS, Buttery PJ. Glucose and amino acids interact with hormones to control expression of insulin-like growth factor-I and growth hormone receptor mRNA in cultured pig hepatocytes. J Nutr 1999;129:1298–1306.
64. Shuto Y, Nakano T, Sanno N, Domoto H, Sugihara H, Wakabayashi I. Clinical case seminar—Reduced growth hormone receptor messenger ribonucleic acid in an aged man with chronic malnutrition and growth hormone resistance. J Clin Endocrinol Metab 1999;84:2320–2323.
65. Hermansson M, Wickelgren RB, Hammarqvist F, Bjarnason R, Wennström I, Carlsson B, et al. Measurement of human growth hormone receptor messenger ribonucleic acid by a quantitative polymerase chain reaction- based assay: Demonstration of reduced expression after elective surgery. J Clin Endocrinol Metab 1997;82:421–428.
66. Ninh NX, Maiter D, Lause P, Chrzanowska B, Underwood LE, Ketelslegers J-M et al. Continuous administration of growth hormone (GH) does not prevent the decrease of IGF-I gene expression in zinc-deprived rats despite normalization of liver GH binding. Growth Regul 1997;7:1–8.
67. Tonshoff B, Eden S, Weiser E, Carlsson B, Robinson IC, Blum WF et al. Reduced hepatic growth hormone (GH) receptor gene expression and increased plasma GH binding protein in experimental uremia. Kidney Int 1994;45:1085–1092.
68. Defalque D, Brandt N, Ketelslegers JM, Thissen JP. GH insensitivity induced by endotoxin injection is associated with decreased liver GH receptors. Am J Physiol 1999;276:E565–E572.
69. Fliesen T, Maiter D, Gerard G, Underwood LE, Maes M, Ketelslegers J-M. Reduction of serum insulin-like growth factor-I by dietary protein restriciton is age dependent. Pediatr Res 1989;26:415–419.

70. Thissen JP, Triest S, Maes M, Underwood LE, Ketelslegers JM. The decreased plasma concentrations of insulin-like growth factor-I in protein-restricted rats is not due to decreased number of growth hormone receptors on isolated hepatocytes. J Endocrinol 1990;124:159–165.
71. Oster MH, Fielder PJ, Levin N, Cronin MJ. Adaptation of the growth hormone and insulin-like growth factor- I axis to chronic and severe calorie or protein malnutrition. J Clin Invest 1995;95:2258–2265.
72. Phillips LS, Goldstein S, Pao CI. Nutrition and somatomedin XXVI. Molecular regulation of IGF-I by insulin in cultured rat hepatocytes. Diabetes 1991;40:1525–1530.
73. Thissen JP, Pucilowska J, Underwood LE. Differential regulation of IGF-I and IGFBP-1 mRNAs by amino acid availability and growth hormone in rat hepatocyte primary culture. Endocrinology 1994;134:1570–1576.
74. Beauloye V, Willems B, de C, V, Frank SJ, Edery M, Thissen JP. Impairment of liver GH receptor signaling by fasting. Endocrinology 2002;143:792–800.
75. Davey HW, Xie T, McLachlan MJ, Wilkins RJ, Waxman DJ, Grattan DR. STAT5b is required for GH-induced liver *Igf*-I gene expression. Endocrinology 2001;142:3836–3841.
76. Nicholson SE, Hilton DJ. The SOCS proteins: a new family of negative regulators of signal transduction. J Leukocyte Biol 1998;63:665–668.
77. Hansen JA, Lindberg K, Hilton DJ, Nielsen JH, Billestrup N. Mechanism of inhibition of growth hormone receptor signaling by suppressor of cytokine signaling proteins. Mol Endocrinol 1999;13:1832–1843.
78. Schaefer F, Chen Y, Tsao T, Nouri P, Rabkin R. Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. J Clin Invest 2001;108:467–475.
79. Mao YL, Ling PR, Fitzgibbons TP, McCowen KC, Frick GP, Bistrian BR et al. Endotoxin-induced inhibition of growth hormone receptor signaling in rat liver in vivo. Endocrinology 1999;140:5505–5515.
80. Phillips LS, Young HS. Nutrition and somatomedin. II. Serum somatomedin activity and cartilage growth activity in streptozotocin-diabetic rats. Diabetes 1976;25:516–527.
81. Scott CD, Baxter RC. Production of insulin-like growth factor-I and its binding protein in rat hepatocytes cultured from diabetic and insulin- treated diabetic rats. Endocrinology 1986;119:2346–2352.
82. Baxter RC, Bryson JM, Turtle JR. Somatogenic receptors of rat liver: regulation by insulin. Endocrinology 1980;107:1176–1181.
83. Tollet P, Enberg B, Mode A. Growth hormone (GH) regulation of cytochrome P-450IIC12, Insulin-like growth factor-I (IGF-I), and GH receptor messenger RNA expression in primary rat hepatocytes: a hormonal interplay with insulin, IGF-I, and thyroid hormone. Mol Endocrinol 1990;4:1934–1942.
84. Maes M, Underwood LE, Ketelslegers J-M. Low serum somatomedin-C in insulin-dependent diabetes: evidence for a postreceptor mechanism. Endocrinology 1986;118:377–382.
85. Johnson TR, Blossey BK, Denko CW, Ilan J. Expression of insulin-like growth factor-I in cultured rat hepatocytes: effects of insulin and growth hormone. Mol Endocrinol 1989;3:580–587.
86. Boni-Schnetzler M, Schmid C, Meier PJ, Froesch ER. Insulin regulates insulin-like growth factor I mRNA in rat hepatocytes. Am J Physiol 1991;260:E846–E851.
87. Houston B, O'Neill IE. Insulin and growth hormone act synergistically to stimulate insulin-like growth factor-I production by cultured chicken hepatocytes. J Endocrinol 1991;128:389–393.
88. Pao CI, Farmer PK, Begovic S, Villafuerte BC, Wu G, Robertson DG, et al. Regulation of Insulin-like growth factor-I (IGF-I) and IGF- binding protein-1 gene transcription by hormones and amino acids in rat hepatocytes. Mol Endocrinol 1993;7:1561–1568.
89. Goya L, De la Puente A, Ramos S, Mart'n MA, Escrivá' F, Alvarez C, et al. Regulation of IGF-I and -II by insulin in primary cultures of fetal rat hepatocytes. Endocrinology 2001;142:5089–5096.
90. Maiter D, Fliesen T, Underwood LE, Maes M, Gerard G, Davenport ML, et al. Dietary protein restriction decreases insulin-like growth factor I independent of insulin and liver growth hormone binding. Endocrinology 1989;124:2604–2611.
91. Caufriez A, Golstein J, Lebrun P, Herchuelz A, Furlanetto R, Copinschi G. Relations between immunoreactive somatomedin-C, insulin and T3 patterns during fasting in obese subjects. Clin Endocrinol (Oxf) 1984;20:65–70.
92. Glas AR, Mellitt R, Burman KD, et al. Serum triiodothyronine in undernourished rats: dependence on dietary composition rather than total calorie or protein intake. Endocrinology 1978;102:1925–1928.

93. Burstein PJ, Draznin B, Johnson CJ, Schalch DS. The effect of hypothyroidism on growth, serum growth hormone, the growth hormone-dependent somatomedin, insulin-like growth factor, and its carrier protein in rats. Endocrinology 1979;104:1107–1111.
94. Harakawa S, Yamashita S, Tobinaga T, Matsuo K, Hirayu H, Izumi M, et al. In vivo regulation of hepatic insulin-like growth factor-I messenger ribonucleic acids with thyroid hormone. Endocrinol Japon 1990;37:205–211.
95. Evans RM, Birnberg NC, Rosenfeld MG. Glucocorticoid and thyroid hormones transcriptionally regulate growth hormone gene expression. Proc Natl Acad Sci USA 1982;79:7659–7663.
96. Wolf M, Ingbar SH, Moses AC. Thyroid hormone and growth hormone interact to regulate insulin-like growth factor-I messenger ribonucleic acid and circulating levels in the rat. Endocrinology 1989;125:2905–2914.
97. keda T, Fujiyama K, Hoshino T, Takeuchi T, Mashiba H, Tominaga M. Possible role of thyroid hormone in decreased somatomedin-C levels in diabetic and starved rats. Ann Nutr Metab 1990;34:8–12.
98. Luo J, Murphy LJ. Dexamethasone inhibits growth hormone induction of insulin-like growth factor-I messenger ribonucleic acid (mRNA) in hypophysectomized rats and reduces IGF-I mRNA abundance in the intact rat. Endocrinology 1989;125:165–171.
99. Jux C, Leiber K, Hügel U, Blum W, Ohlsson C, Klaus G, et al. Dexamethasone impairs growth hormone (GH)-stimulated growth by suppression of local insulin-like growth factor (IGF)-I production and expression of GH- and IGF-I-receptor in cultured rat chondrocytes. Endocrinology 1998;139:3296–3305.
100. King APJ, Carter-Su C. Dexamethasone-induced antagonism of growth hormone (GH) action by down-regulation of GH binding in 3T3–F442A fibroblasts. Endocrinology 1995;136:4796–4803.
101. Rodgers BD, Lau AOT, Nicoll CS. Hypophysectomy or adrenalectomy of rats with insulin-dependent diabetes mellitus partially restores their responsiveness to growth hormone. Proc Soc Exp Biol Med 1994;207:220–226.
102. Bryson JM, Baxter RC. Adrenal involvement in the diabetes-induced loss of Growth Hormone and Prolactin receptors in the livers of female rats. Diabetologia 1986;29:106–111.
103. Unterman TG, Jentel JJ, Oehler DT, Lacson RG, Hofert JF. Effects of glucocorticoids on circulating levels and hepatic expression of insulin-like growth factor (IGF)-binding proteins and IGF-I in the adrenalectomized streptozotocin-diabetic rat. Endocrinology 1993;133(6):2531–2539.
104. Fan J, Char D, Bagby GJ, Gelato MC, Lang CH. Regulation of insulin-like growth factor- I (IGF-I) and IGF binding proteins by tumor necrosis factor. Am J Physiol 1995;269:R1204–R1212.
105. Lang CH, Fan J, Cooney R, Vary TC. IL-1 receptor antagonist attenuates sepsis-induced alterations in the IGF system and protein synthesis. Am J Physiol Endocrinol Metab 1996;270:E430–E437.
106. Thissen JP, Verniers J. Inhibition by interleukin-1β and tumor necrosis factor-a of the insulin-like growth factor I messenger ribonucleic acid response to growth hormone in rat hepatocyte primary culture. Endocrinology 1997;138:1078–1084.
107. Maniar S, Kleinknecht C, Zhou X, Motel V, Yvert JP, Dechaux M. Growth hormone action is blunted by acidosis in experimental uremia or acid load. Clin Nephrol 1996;46:72–76.
108. Bereket A, Wilson TA, Kolasa AJ, Fan J, Lang CH. Regulation of the insulin-like growth factor system by acute acidosis. Endocrinology 1996;137:2238–2245.
109. Harp JB, Goldstein S, Phillips LS. Molecular regulation of IGF-I by amino acid availability in cultured hepatocytes. Diabetes 1991;40:95–101.
110. Wheelhouse NM, Stubbs AK, Lomax MA, MacRae JC, Hazlerigg DG. Growth hormone and amino acid supply interact synergistically to control insulin-like growth factor-I production and gene expression in cultured ovine hepatocytes. J Endocrinol 1999;163:353–361.
111. Zhang JH, Chrysis D, Underwood LE. Reduction of hepatic insulin-like growth factor I (IGF-I) messenger ribonucleic acid (mRNA) during fasting is associated with diminished splicing of IGF-I pre-mRNA and decreased stability of cytoplasmic IGF-I mRNA. Endocrinology 1998;139:4523–4530.
112. Phillips LS, Huang S. Identification of an amino acid responsive element in the rat IGF-I gene. 10th International Congress of Endocrinology, June 12–15, 1966, San Francisco, CA.
113. Fafournoux P, Bruhat A, Jousse C. Amino acid regulation of gene expression. Biochem J 2000;351:1–12.
114. Dudek SM, Semenkovich CF. Essential amino acids regulate fatty acid synthase expression through an uncharged transfer RNA-dependent mechanism. J Biol Chem 1995;270:29323–29329.

115. Jousse C, Bruhat A, Ferrara M, Fafournoux P. Physiological concentration of amino acids regulates insulin- like-growth-factor-binding protein 1 expression. Biochemical J 1998;334:147–153.
116. Takenaka A, Oki N, Takahashi SI, Noguchi T. Dietary restriction of single essential amino acids reduces plasma insulin-like growth factor-I (IGF-I) but does not affect plasma IGF-binding protein-1 in rats. J Nutr 2000;130:2910–2914.
117. Goya L, De la Puente A, Ramos S, Mart'n MA, Escrivá F, Pascual-Leone AM. Regulation of insulin-like growth factor-I and -II by glucose in primary cultures of fetal rat hepatocytes. J Biol Chem 1999;274:24633–24640.
118. Lefebvre D, Beckers F, Ketelslegers JM, Thissen JP. Zinc regulation of insulin-like growth factor-I (IGF-I), growth hormone receptor (GHR) and binding protein (GHBP) gene expression in rat cultured hepatocytes. Mol Cell Endocrinol 1998;138:127–136.
119. Emler CA, Schalch DS. Nutritionally-induced changes in hepatic insulin-like growth factor-I (IGF-I) gene expression in rats. Endocrinology 1987;120:832–834.
120. Moats-Staats BM, Brady JLJ, Underwood LE, D'Ercole AJ. Dietary protein restriction in artificially reared neonatal rats causes a reduction of insulin-like growth factor-I gene expression. Endocrinology 1989;125:2368–2374.
121. Straus DS, Takemoto CD. Specific decrease in liver insulin-like growth factor-I and brain insulin-like growth factor-II gene expression in energy- restricted rats. J Nutr 1991;121:1279–1286.
122. Thissen JP, Triest S, Moats-Staats BM, Underwood LE, Mauerhoff T, Maiter D et al. Evidence that pretranslational and translational defects decrease serum IGF-I concentrations during dietary protein restriction. Endocrinology 1991;129:429–435.
123. Lowe WL, Jr., Adamo M, Werner H, Roberts CT, Jr., LeRoith D. Regulation by fasting of rat insulin-like growth factor I and its receptor. Effects on gene expression and binding. J Clin Invest 1989;84:619–626.
124. Adamo M, Ben-Hur H, Roberts CT, Jr., LeRoith D. Regulation of start site usage in the leader exons of the rat insulin-like growth factor-I gene by development, fasting, and diabetes. Molecular Endocrinology 1991;5:1677–1686.
125. Zhang JH, Whitehead RE, Jr., Underwood LE. Effect of fasting on insulin-like growth factor (IGF)-IA and IGF-IB messenger ribonucleic acids and prehormones in rat liver. Endocrinology 1997;138:3112–3118.
126. Straus DS, Takemoto CD. Effect of dietary protein deprivation on insulin-like growth factor-I and -II, IGF binding protein-2, and serum albumin gene expression in rat. Endocrinology 1990;127:1849–1860.
127. Hayden JM, Marten NW, Burke EJ, Straus DS. The effect of fasting on insulin-like growth factor-I nuclear transcript abundance in rat liver. Endocrinology 1994;134:760–768.
128. Hayden JM, Straus DS. IGF-I and serine protease inhibitor 2.1 nuclear transcript abundance in rat liver during protein restriction. J Endocrinol 1995;145:397–407.
129. Marten NW, Sladek FM, Straus DS. Effect of dietary protein restriction on liver transcription factors. Biochem J 1996;317:361–370.
130. Marten NW, Hsiang CH, Yu L, Stollenwerk NS, Straus DS. Functional activity of hepatocyte nuclear factor-1 is specifically decreased in amino acid-limited hepatoma cells. Biochim Biophys Acta 1999;1447:160–174.
131. Marten NW, Burke EJ, Hayden JM, Straus DS. Effect of amino acid limitation on the expression of 19 genes in rat hepatoma cells. FASEB J 1994;8:538–544.
132. Entingh AJ, Law BK, Moses HL. Induction of the C/EBP homologous protein (CHOP) by amino acid deprivation requires insulin-like growth factor I, phosphatidylinositol 3-kinase, and mammalian target of rapamycin signaling. Endocrinology 2001;142:221–228.
133. Ron D, Habener JF. CHOP, a novel developmentally regulated nuclear protein that dimerizes with transcription factors C/EBP and LAP and functions as a dominant- negative inhibitor of gene transcription. Genes Dev 1992;6:439–453.
134. Nolten LA, van Schaik FM, Steenbergh PH, Sussenbach JS. Expression of the insulin-like growth factor I gene is stimulated by the liver-enriched transcription factors C/EBP alpha and LAP. Mol Endocrinol 1994;8:1636–1645.
135. Nolten LA, Steenbergh PH, Sussenbach JS. Hepatocyte nuclear factor 1 alpha activates promoter 1 of the human insulin-like growth factor I gene via two distinct binding sites. Mol Endocrinol 1995;9:1488–1499.

136. Zhu JL, Kaytor EN, Pao CI, Meng XP, Phillips LS. Involvement of Sp1 in the transcriptional regulation of the rat insulin- like growth factor-1 gene. Mol Cell Endocrinol 2000;164:205–218.
137. Leung-Pineda V, Kilberg MS. Role of Sp1 and Sp3 in the Nutrient-regulated Expression of the Human Asparagine Synthetase Gene. J Biol Chem 2002;277:16585–16591.
138. Hoyt EC, Hepler JE, Van Wyk JJ, Lund PK. Structural characterization of exon 6 of the rat IGF-I gene. DNA and cell biology 1992;11:433–441.
139. Klausner RD, Harford JB. Cis-trans models for post-transcriptional gene regulation. Science 1989;246:870–872.
140. Davenport ML, D'Ercole AJ, Underwood LE. Effect of maternal fasting on fetal growth, serum insulin-like growth factors (IGFs), and tissue IGF messenger ribonucleic acids. Endocrinology 1990;126:2062–2067.
141. Goldstein S, Harp JB, Phillips LS. Nutrition and Somatomedin XXII: molecular regulation of insulin-like growth factor-I during fasting and refeeding in rats. J Molecular Endocrinology 1991;6:33–43.
142. Katsumata M, Kawakami S, Kaji Y, Takada R, Dauncey MJ. Differential regulation of porcine hepatic IGF-I mRNA expression and plasma IGF-I concentration by a low lysine diet. J Nutr 2002;132:688–692.
143. Thissen JP, Underwood LE. Translational status of the Insulin-like growth factor-I mRNAS in liver of protein-restricted rats. J Endocrinol 1992;132:141–147.
144. VandeHaar M, Moats-Staats BM, Davenport ML, Walker JL, Ketelslegers JM, Sharma BK, et al. Reduced serum concentrations of insulin-like growth factor-I (IGF-I) in protein-restricted growing rats are accompanied by reduced IGF-I mRNA levels in liver and skeletal muscle. J Endocrinol 1991;130:305–312.
145. Naranjo WM, Yakar S, Sanchez-Gomez M, Perez AU, Setser J, LeRoith D. Protein calorie restriction affects nonhepatic igf-I production and the lymphoid system: studies using the liver-specific igf-I gene-deleted mouse model. Endocrinology 2002;143:2233–2241.
146. Hintz RL, Liu F. Demonstration of specific plasma protein binding for somatomedin. J Clin Endocrinol Metab 1977;45:988–995.
147. Kaufmann U, Zapf J, Torretti B, Froesch ER. Demonstration of a specific serum carrier protein of nonsuppressible insulin-like activity in vivo. J Clin Endocrinol Metab 1977;44:160–165.
148. Furlanetto RW, Underwood LE, Van Wyk JJ, D'Ercole AJ. Estimation of somatomedin-C levels in normals and patients with pituitary disease by radioimmunoassay. J Clin Invest 1977;60:648–657.
149. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: Biological actions. Endocr Rev 1995;16:3–34.
150. Elgin RG, Busby WHJ, Clemmons DR. An insulin-like growth factor (IGF) binding protein enhances the biologic response to IGF-I. Proc Natl Acad Sci USA 1987;84:3254–3258.
151. Blum WF, Jenne EW, Reppin F, Kietzmann K, Ranke MB, Bierich JR. Insulin-like growth factor I (IGF-I)-binding protein complex is a better mitogen than free IGF-I. Endocrinology 1989;125:766–772.
152. Ernst M, Rodan GA. Increased activity of insulin-like growth factor (IGF) in osteoblastic cells in the presence of growth hormone (GH): positive correlation with the presence of the GH-induced IGF-binding protein BP-3. Endocrinology 1990;127:807–814.
153. Burch WW, Correa J, Shively JE, Powell DR. The 25-kilodalton insulin-like growth factor (IGF)-binding protein inhibits both basal and IGF-I-mediated growth of chick embryo pelvic cartilage in vitro. J Clin Endocrinol Metab 1990;70:173–180.
154. Ross M, Francis GL, Szabo L, Wallace JC, Ballard FJ. Insulin-like growth factor (IGF)-binding proteins inhibit the biological activities of IGF-I and IGF-II but not des(1–3)IGF-I. Biochem J 1989;258:267–272.
155. De Mellow JS, Baxter RC. Growth hormone dependent insulin-like growth factor binding protein both inhibits and potentiates IGF-I stimulated DNA synthesis in skin fibroblasts. Biochem Biophys Res Commun 1988;156:199–204.
156. Frystyk J, Gronbæk H, Skjærbæk C, Flyvbjerg A, Orskov H, Baxter RC. Developmental changes in serum levels of free and total insulin- like growth factor I (IGF-I), IGF-Binding protein-1 and -3, and the acid-labile subunit in rats. Endocrinology 1998;139:4286–4292.
157. Binoux M, Hossenlopp P. Insulin-like growth factor (IGF) and IGF-binding proteins: comparison of human serum and lymph. J Clin Endocrinol Metab 1988;67:509–514.

158. Zapf J, Hauri C, Waldvogel M, Froesch ER. Acute metabolic effects and half-lives of intravenously administered insulinlike growth factors I and II in normal and hypophysectomized rats. J Clin Invest 1986;77:1768–1775.
159. Guler HP, Zapf J, Schmid C, Froesch ER . Insulin-like growth factor-I and II in healthy man. Acta Endocrinol (Copenh) 1989;121:753–758.
160. Frystyk J, Hussain M, Skjaerbaek C, Porksen N, Froesch ER, Orskov H. The pharmacokinetics of free insulin-like growth factor-I in healthy subjects. Growth Horm IGF Res 1999;9:150–156.
161. Bar RS, Clemmons DR, Boes M, Busby WH, Booth BA, Dake BL et al. Transcapillary permeability and subendothelial distribution of endothelial and amniotic fluid insulin-like growth factor binding proteins in the rat heart. Endocrinology 1990;127:1078–1086.
162. Katz LE, DeLeon DD, Zhao H, Jawad AF. Free and Total Insulin-Like Growth Factor (IGF)-I Levels Decline during Fasting: Relationships with Insulin and IGF-Binding Protein-1. J Clin Endocrinol Metab 2002;87:2978–2983.
163. Frystyk J, Grofte T, Skjaerbaek C, Orskov H. The effect of oral glucose on serum free insulin-like growth factor-I and -II in health adults. J Clin Endocrinol Metab 1997;82:3124–3127.
164. Oh Y, Muller HL, Pham H, Rosenfeld RG. Demonstration of receptors for insulin-like growth factor binding protein-3 on Hs578T human breast cancer cells. J Biol Chem 1993;268:26045–26048.
165. Hwa V, Oh Y, Rosenfeld RG. The insulin-like growth factor-binding protein (IGFBP) superfamily. Endocr Rev 1999;20:761–787.
166. Baxter RC, Martin JL. Radioimmunoassay of growth hormone-dependent insulinlike growth factor binding protein in human plasma. J Clin Invest 1986;78:1504–1512.
167. Baxter RC, Cowell CT. Diurnal rhythm of growth hormone-independent binding protein for insulin-like growth factors in human plasma. J Clin Endocrinol Metab 1987;65:432–440.
168. Busby WH, Snyder DK, Clemmons DR. Radioimmunoassay of a 26,000-dalton plasma insulin-like growth factor-binding protein: control by nutritional variables. J Clin Endocrinol Metab 1988;67:1225–1230.
169. Suikkari AM, Koivisto VA, Rutanen EM, Yki-Jarvinen H, Karonen SL, Seppala M. Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. J Clin Endocrinol Metab 1988;66:266–272.
170. Conover CA, Butler PC, Wang M, Rizza RA, Lee PDK. Lack of growth hormone effect on insulin-associated suppression of insulin-like growth factor binding protein-1 in humans. Diabetes 1990;39:1251–1256.
171. Snyder DK, Clemmons DR. Insulin-dependent regulation of insulin-like growth factor- binding protein-1. J Clin Endocrinol Metab 1991;71:1632–1636.
172. Lewitt MS, Baxter RC. Inhibitors of glucose uptake stimulate the production of insulin- like growth factor-binding protein (IGFBP-1) by human fetal liver. Endocrinology 1990;126:1527–1533.
173. Bar RS, Boes M, Clemmons DR, Busby WH , Sandra A, Dake BL et al. Insulin differentially alters transcapillary movement of intravascular IGFBP-1, IGFBP-2 and endothelial cell IGF-binding proteins in the rat heart. Endocrinology 1990;127:497–499.
174. Clemmons DR, Snyder DK, Busby WH. Variables controlling the secretion of insulin-like growth factor binding protein-2 in normal human subjects. J Clin Endocrinol Metab 1991;73:727–733.
175. Orlowski CC, Brown AL, Ooi GT, Yang YWH, Tseng LYH, Rechler MM. Tissue, developmental, and metabolic regulation of messenger ribonucleic acid encoding a rat insulin-like growth factor-binding proteins. Endocrinology 1990;126:644–652.
176. Murphy LJ, Seneviratne C, Moreira P, Reid RE. Enhanced expression of insulin-like growth factor-binding protein-1 in the fasted rat: the effects of insulin and growth hormone administration. Endocrinology 1991;128:689–696.
177. Tseng LYH, Ooi GT, Brown AL, Straus DS, Rechler MM. Transcription of the insulin-like growth factor-binding protein-2 is increased in neonatal and fasted rat liver. Mol Endocrinol 1992;6:1195–1201.
178. Smith WJ, Underwood LE, Clemmons DR. Effects of caloric or protein restriction on insulin-like growth factor-I (IGF-I) and IGF-binding proteins in children and adults. J Clin Endocrinol Metab 1995;80:443–449.
179. Gallaher BW, Breier BH, Oliver MH, Harding JE, Gluckman PD. Ontogenic differences in the nutritional regulation of circulating IGF binding proteins in sheep plasma. Acta Endocrinol (Copenh) 1992;126:49–54.

180. Frystyk J, Delhanty PJD, Skjærbæk C, Baxter RC. Changes in the circulating IGF system during short-term fasting and refeeding in rats. Am J Physiol Endocrinol Metab 1999;277:E245–E252.
181. Baxter RC, Martin JL, Tyler MI, Howden MEH. Growth hormone-dependent insulin-like growth factor (IGF) binding protein from human plasma differs from other human IGF binding proteins. Biochem Biophys Res Commun 1986;139:1256–1261.
182. McCusker RH, Cohick WS, Busby WH, Clemmons DR. Evaluation of the developmental and nutritional changes in porcine IGFBP-1 and IGFBP-2 serum levels by immunoassay. Endocrinology 1991;129:2631–2638.
183. Donovan SM, Atilano LC, Hintz RL, Wilson DM, Rosenfeld RG. Differential regulation of the insulin-like growth factors (IGF- I and -II) and IGF binding proteins during malnutrition in the neonatal rat. Endocrinology 1991;129:149–157.
184. Davenport ML, Clemmons DR, Miles MV, Camacho-Hubner C, D'Ercole AJ, Underwood LE. Regulation of serum insulin-like growth factor I (IGF-I) and IGF binding proteins during rat pregnancy. Endocrinology 1990;127:1278–1286.
185. Davenport ML, Isley WL, Pucilowska JB, Pemberton LB, Lyman B, Underwood LE et al. Insulin-like growth factor binding protein-3 proteolytic activity is induced following elective surgery. J Clin Endocrinol Metab 1992;75:590–595.
186. Timmins AC, Cotterill AM, Hughes SCC, Holly JMP, Ross RJM, Blum W, et al. Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and -II, alterations in insulin-like growth factor binding proteins, and induction of an insulin-like growth factor binding protein 3 protease. Crit Care Med 1996;24:1460–1466.
187. Stoving RK, Flyvbjerg A, Frystyk J, Fisker S, Hangaard J, Hansen-Nord M et al. Low serum levels of free and total insulin-like growth factor I (IGF-I) in patients with anorexia nervosa are not associated with increased IGF-binding protein-3 proteolysis. J Clin Endocrinol Metab 1999;84:1346–1350.
188. Dai J, Baxter RC. Regulation in vivo of the acid-labile subunit of the rat serum insulin-like growth factor-binding protein complex. Endocrinology 1994;135:2335–2341.
189. Oster MH, Levin N, Fielder PJ, Robinson ICAF, Baxter RC, Cronin MJ. Developmental differences in the IGF-I system response to severe and chronic calorie malnutrition. Am J Physiol Endocrinol Metab 1996;270:E646–E653.
190. Takenaka A, Mori M, Yamada S, Ohgane J , Takahashi SI, Noguchi T. Nutritional regulation of gene expression of insulin-like growth factor-binding proteins and the acid-labile subunit in various tissues of rats. J Endocrinol 1996;150:33–41.
191. Dai J, Scott CD, Baxter RC. Regulation of the acid-labile subunit of the insulin-like growth factor complex in cultured rat hepatocytes. Endocrinology 1994;135:1066–1072.
192. Bereket A, Wilson TA, Blethen SL, Sakurai Y, Herndon DN, Wolfe RR, et al. Regulation of the acid-labile subunit of the insulin-like growth factor ternary complex in patients with insulin-dependent diabetes mellitus and severe burns. Clin Endocrinol (Oxf ) 1996;44:525–532.
193. Thissen JP, Underwood LE, Maiter D, Maes M, Clemmons DR, Ketelslegers JM. Failure of IGF-I infusion to promote growth in protein- restricted rats despite normalization of serum IGF-I concentrations. Endocrinology 1991;128:885–890.
194. Lemozy S, Pucilowska JB, Underwood LE. Reduction of insulin-like growth factor-I (IGF-I) in protein-restricted rats is associated with differential regulation of IGF- binding protein messenger ribonucleic acids in liver and kidney, and peptides in liver and serum. Endocrinology 1994;135:617–623.
195. Skjaerbaek C, Frystyk J, Orskov H, Kissmeyer-Nielsen P, Jensen MB, Laurberg S et al. Differential changes in free and total insulin-like growth factor I after major, elective abdominal surgery: the possible role of insulin- like growth factor-binding protein-3 proteolysis. J Clin Endocrinol Metab 1998;83:2445–2449.
196. Lang CH, Pollard V, Fan J, Traber LD, Traber DL, Frost RA, et al. Acute alterations in growth hormone insulin-like growth factor axis in humans injected with endotoxin. Am J Physiol Regul Integr Comp Physiol 1997;273:R371–R378.
197. Lang CH, Fan J, Frost RA, Gelato MC, Sakurai Y, Herndon DN et al. Regulation of the insulin-like growth factor system by insulin in burn patients. J Clin Endocrinol Metab 1996;81:2474–2480.
198. Takahashi S, Kajikawa M, Umezawa T, Takahashi SI, Kato H, Miura Y et al. Effect of dietary proteins on the plasma immunoreactive insulin- like growth factor-I/somatomedin-C concentrations in the rat. Br J Nutr 1990;63:521–534.

199. Thissen JP, Davenport ML, Pucilowska J, Miles MV, Underwood LE. Increased serum clearance and degradation of [125I]-labeled IGF- I in protein-restricted rats. Am J Physiol 1992;262:E406–E411.
200. Cohen KL, Nissley SP. The serum half-life of somatomedin activity: evidence for growth hormone dependence. Acta Endocrinol (Copenh) 1976;83:243–258.
201. Fan J, Char D, Kolasa AJ, Pan W, Maitra SR, Patlak CS et al. Alterations in hepatic production and peripheral clearance of IGF-I after endotoxin. Am J Physiol Endocrinol Metab 1995;269:E33–E42.
202. Ninh NX, Maiter D, Verniers J, Lause P , Ketelslegers JM, Thissen JP. Failure of exogenous IGF-I to restore normal growth in rats submitted to dietary zinc deprivation. J Endocrinol 1998;159:211–217.
203. Bourrin S, Ammann P, Bonjour JP, Rizzoli R. Dietary protein restriction lowers plasma insulin-like growth factor I (IGF-I), impairs cortical bone formation, and induces osteoblastic resistance to IGF-I in adult female rats. Endocrinology 2000;141:3149–3155.
204. Kee AJ, Baxter RC, Carlsson AR, Smith RC. Parenteral amino acid intake alters the anabolic actions of insulin- like growth factor I in rats. Am J Physiol 1999;277:E63–E72.
205. Philipps AF, Persson B, Hall K, Lake M , Skottner A, Sanengen T et al. The effects of biosynthetic insulin-like growth factor-I supplementation on somatic growth, maturation, and erythropoiesis on the neonatal rat. Pediatr Res 1988;23:298–305.
206. Hirschberg R, Kopple JD. Evidence that insulin-like growth factor-I increases renal plasma flow and glomerular filtration rate in fasted rats. J Clin Invest 1989;83:326–330.
207. Jacob R, Barrett E, Plewe G, Fagin KD, Sherwin RS. Acute effects of insulin-like growth factor-I on glucose and amino acid metabolism in the awake fasted rat. J Clin Invest 1989;83:1717–1723.
208. Tomas FM, Knowles SE, Owens PC, Read LC, Chandler CS, Gargowsky SE et al. Effects of full-length and truncated insulin-like growth factor- I on nitrogen balance and muscle protein metabolism in nitrogen- restricted rats. J Endocrinol 1991;128:97–105.
209. Dardevet D, Manin M, Balage M, Sornet C, Grizard J. Influence of low- and high-protein diets on insulin and insulin- like growth factor-I binding to skeletal muscle and liver in the growing rats. Br J Nutr 1991;65:47–60.
210. Lefebvre D, Boney CM, Ketelslegers JM, Thissen JP. Inhibition of insulin-like growth factor-I mitogenic action by zinc chelation is associated with a decreased mitogen-activated protein kinase activation in RAT-1 fibroblasts. FEBS Lett 1999;449:284–288.
211. Patti ME, Brambilla E, Luzi L, Landaker EJ, Kahn CR. Bidirectional modulation of insulin action by amino acids. J Clin Invest 1998;101:1519–1529.
212. Balage M, Sinaud S, Prod'homme M, Dardevet D, Vary TC, Kimball SR et al. Amino acids and insulin are both required to regulate assembly of the eIF4E.eIF4G complex in rat skeletal muscle. Am J Physiol Endocrinol Metab 2001;281:E565–E574.
213. Snyder DK, Clemmons DR, Underwood LE. Treatment of obese, diet-restricted subjects withg growth hormone for 11 weeks: effects of anabolism, lipolysis, and body composition. J Clin Endocrinol Metab 1988;67:54–61.
214. Clemmons DR, Smith-Banks A, Underwood LE. Reversal of diet-induced catabolism by infusion of recombinant Insulin-like growth factor-I (IGF-I) in humans. J Clin Endocrinol Metab 1992;75:234–238.
215. Mauras N, Beaufrere B. Recombinant human IGF-I enhances whole body protein anabolism and significantly diminishes the protein catabolic effect of prednisone in humans without a diabetogenic effect. J Clin Endocrinol Metab 1995;80:869–874.
216. Kupfer SR, Underwood LE, Baxter RC, Clemmons DR. Enhancement of the anabolic effects of growth hormone and insulin-like growth factor-I by use of both agent simultaneously. J Clin Invest 1993;91:391–396.
217. McNurlan MA, Garlick PJ, Steigbigel RT, DeCristofaro KA, Frost RA, Lang CH et al. Responsiveness of muscle protein synthesis to growth hormone administration in HIV-infected individuals declines with severity of disease. J Clin Invest 1997;100:2125–2132.
218. Vary TC, Dardevet D, Grizard J, Voisin L, Buffiere C, Denis P et al. Differential regulation of skeletal muscle protein turnover by insulin and IGF-I after bacteremia. Am J Physiol 1998;275:E584–E593.
219. Fouque D, Peng SC, Kopple JD. Impaired metabolic response to recombinant insulin-like growth factor-1 in dialysis patients. Kidney Int 1995;47:876–883.

220. Ding H, Gao XL, Hirschberg R, Vadgama JV, Kopple JD. Impaired actions of insulin-like growth factor 1 on protein Synthesis and degradation in skeletal muscle of rats with chronic renal failure. Evidence for a postreceptor defect. J Clin Invest 1996;97:1064–1075.
221. Fang CH, Li BG, Sun X, Hasselgren PO. Insulin-like growth factor I reduces ubiquitin and ubiquitin-conjugating enzyme gene expression but does not inhibit muscle proteolysis in septic rats. Endocrinology 2000;141:2743–2751.
222. Fang CH, Li BG, Wang JJ, Fischer JE, Hasselgren PO. Treatment of burned rats with insulin-like growth factor I inhibits the catabolic response in skeletal muscle. Am J Physiol Regul Integr Comp Physiol 1998;275:R1091–R1098.



http://www.springer.com/978-1-58829-190-5

IGF and Nutrition in Health and Disease

Houston, M.S.; Holly, J.M.P.; Feldman, E.L. (Eds.)

2004, XXI, 359 p., Hardcover
ISBN: 978-1-58829-190-5
A product of Humana Press