Lead Review Article

Regulation of Insulin-like Growth Factor–I in Starvation and Injury
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Both starvation and sepsis are characterized by growth hormone (GH) insensitivity, which leads to a reduction in circulating insulin-like growth factor (IGF)-I. Because of the anabolic properties of this growth factor, its decline may contribute to the growth arrest and the catabolic reaction observed in starvation and sepsis. This review focuses on the mechanisms responsible for the reduction in circulating IGF-I and impairment of GH responsiveness that occur during starvation and sepsis. A clearer understanding of the complex nature of GH resistance should lead to the development of new therapeutic strategies aimed at restoring the beneficial effects of anabolic agents such as GH and IGF-I.

Introduction

A decrease in body cell mass occurs during both starvation and sepsis. In the nutritionally deprived patient, insufficient intake of energy and amino acids, with secondary changes in the hormonal milieu, is the principal mechanism of loss of cell mass. This form of malnutrition, which is characterized by substantial fat loss and a less severe lean tissue loss, responds quickly to complete nutritional support. By contrast, in the critically ill patient with severe injury or infection an increase in the rate of protein catabolism caused by a systemic inflammatory response is responsible for the decline in cell mass. This malnutrition, which occurs despite adequate feeding, is thought to be secondary to cytokine production.

In both situations the circulating concentrations of insulin-like growth factor (IGF-I), an anabolic hormone, are decreased. Because of its stimulatory effect on protein synthesis and its inhibitory effect on protein catabolism, this decline in IGF-I might contribute to the loss of body cell mass in these clinical situations. This review presents the current understanding of the mechanisms responsible for the decrease in IGF-I in both conditions. Data from human studies and animal experiments are discussed.

IGF-I (formerly, somatomedin-C) is a single-chain polypeptide produced primarily by the liver. Growth hormone (GH) is the principal hormonal stimulus for IGF-I production, while IGF-I inhibits GH release by the pituitary by negative feedback. Some of the GH in the circulation is bound to a specific GH-binding protein (GHBP) that corresponds to the extracellular domain of the GH receptor (GHR). IGF-I mediates most of the anabolic actions of GH, promotes the growth of most cell types, and together with other growth factors, stimulates cellular differentiation and differentiated functions of specialized cells. In addition to its anabolic properties, IGF-I exerts multiple insulin-like metabolic effects. Its infusion decreases blood glucose, inhibits lipolysis, and retards protein breakdown. In serum and most body fluids, IGF-I is complexed with high-affinity binding proteins (IGFBPs). Most IGF-I circulates as a 150-kDa complex consisting of IGF-I, IGFBP-3, and an acid-labile subunit (ALS). The remainder of bound IGF-I circulates as a 30- to 40-kDa complex (IGF-I bound to IGFBP-1, -2, or -4). Each of these binding proteins is regulated differently and is believed to modulate the actions of IGF-I. The actions of IGF-I are mediated mainly by the type 1 IGF receptor. This receptor has a tyrosine kinase subunit similar to that of the insulin receptor and is present on virtually all cell types.

Evidence for the Nutritional Regulation of IGF-I in Humans

Fasting and Malnutrition

Fasting in normal volunteers causes serum IGF-I to decline within 24 hours and to reach 20% of prefast values by 10 days. Changes in serum IGF-I concentrations parallel changes in nitrogen balance, suggesting that decreased IGF-I in serum might mediate a decline in protein
serum IGF-I is not restricted to fasting but is also observed in protein-calorie malnutrition (marasmus, kwashiorkor, anorexia nervosa, celiac disease, AIDS, inflammatory bowel diseases, etc.). In general, the magnitude of IGF-I reduction relates to the severity of the nutritional insult as assessed by serum albumin concentration, weight deficit, or body cell mass loss. GH secretion is often increased in malnourished patients, suggesting that these patients have resistance to the action of GH. Pharmacologic doses of GH, however, may still increase IGF-I and cause nitrogen retention in some malnourished patients.

**Respective Role of Energy and Protein Intake**

Both energy and protein appear to be important in regulating serum IGF-I because each is essential to the restoration of serum IGF-I concentrations after fasting. Refeeding a normocaloric and normoproteic diet raises IGF-I to nearly 70% of the basal prefast values by the fifth day, whereas refeeding a protein-deficient isocaloric diet results in a 2-day delay in the upward inflection of IGF-I and increases IGF-I to only 50% of control prefast values. By contrast, a diet deficient in both protein and energy causes a further decrease of IGF-I (Figure 1). The importance of energy intake in regulating IGF-I is supported by the existence of a threshold of energy requirement (11 kcal/kg/day), below which optimal protein intake fails to raise IGF-I after fasting. 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 responsiveness of IGF-I to GH when energy intake is severely restricted. 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 are restored more readily after fasting by a protein-restricted diet rich in essential amino acids than one that is rich in nonessential amino acids.

**Mechanisms Involved in the Nutritional Regulation of IGF-I Production**

**Role of Secretion and Hypothalamic Regulation of GH**

Because pituitary GH is the principal stimulus of IGF-I production, impaired GH secretion may cause decreased serum IGF-I concentrations when food intake decreases. In rats, the pulsatile secretion of GH is dramatically reduced by decreased availability of nutrients. Decreased GH secretion could thereby be responsible for the decline of serum IGF-I. Unlike rats, however, humans have increased GH secretion during dietary restriction. This suggests 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 inhibitory somatostatin (SRIH [somatotropine-releasing inhibitory hormone]) tone or from reduced growth hormone-releasing hormone (GHRH) stimulation of somatotroph cells. 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. The decline in GH secretion during fasting could result also from diminished GHRH secretion because levels of GHRH mRNA in the hypothalamus are decreased dramatically after 72 hours of fasting. The protein content of the diet seems to be critical for the regulation of hypothalamic GHRH gene expression. In addition to GHRH and SRIH, leptin probably plays a major role in the decline of GH secretion during fasting in rats. Administration of leptin antiserum to normal rats leads to a clear-cut decrease in plasma GH levels. Furthermore, GH secretion is restored to normal in fasted rats after intracerebroventricular injection of leptin. This effect is probably mediated by inhibition of the secretion of NPY, a neuropeptide that strongly inhibits GH secretion. The GH secretion is also impaired in several other models of dietary manipulation in rats that are associated with growth retardation and low serum IGF-I concentrations.

The mechanisms responsible for increased GH secretion in response to dietary restriction in other species are less clear. Reduction of hypophyseal portal venous blood concentrations of SRIH, decreased metabolic clearance...
rate of GH, and reduced peripheral plasma IGF-I may contribute to the high GH concentrations. Despite increased GH secretion, however, serum IGF-I is reduced, suggesting that the production mechanisms for IGF-I in tissues are insensitive to GH in undernourished animals.

**Role of GH Receptor and Postreceptor Defects**

Because the liver is the major site for the production of circulating IGF-I, reduction of liver GH binding capacity could cause impaired production of IGF-I and decreased serum concentrations. During fasting and refeeding, there is a close temporal relationship between serum IGF-I concentrations and the number of hepatic somatogenic (GH) binding sites. Reduction in hepatic GH binding capacity, therefore, could be one mechanism responsible for the fasting-induced decline in IGF-I.

The role of the liver GH receptors in the decline of serum IGF-I in protein-restricted rats is more questionable. The relationships between serum IGF-I and GH binding sites were assessed in rats subjected to dietary protein restriction (5% versus 15% protein in the diet). Feeding a low-protein diet for 24 hours caused a dramatic decrease in serum IGF-I, but only a modest decrease in liver GH binding sites. In older animals, protein restriction for 7 days also caused a decline in serum IGF-I without reduction of GH binding to liver membranes or to freshly isolated hepatocytes. Furthermore, the serum IGF-I response to a single injection of GH in hypophysectomized protein-restricted rats was severely blunted compared with control rats, despite comparable numbers of liver GH binding sites in the two dietary groups. Finally, even though continuous GH infusion in protein-restricted rats increased liver GH binding sites to the level of control-fed rats, serum IGF-I was not increased. Taken together, these studies, which show discordance between normal liver GH binding and low IGF-I, suggest that the GH resistance in protein-restricted rats is caused by a post-receptor defect. The intracellular defect in GH action could be a direct effect of limited nutrients or could result from hormonal changes. GH resistance associated with decrease of liver GH binding is present also in other dietary models of malnutrition, such as zinc deficiency.

Differential regulation of the GH receptor in fasting and protein restriction has been confirmed at the molecular level. GH receptor gene expression is reduced in parallel with liver GH binding, confirming at the mRNA level the changes observed at the level of GH receptor binding.

In the rat, GHBP is synthesized from an alternatively spliced mRNA in which exons that encode the transmembrane and cytosolic domains of GHR are replaced with exons that encode a hydrophilic peptide. Dietary restriction causes parallel decrease of liver GH binding and serum GHBP. The role of the circulating GHBP in the control of the GH action is still disputed.

**Role of Hormones**

Dietary restriction causes serum insulin concentrations to decline; insulin-deficient diabetic rats have low serum IGF-I associated with decreased liver GH binding. Insulin replacement restores both to normal. This suggests that insulin may regulate serum IGF-I concentrations, perhaps through changes in the liver GH binding. Supporting the latter hypothesis is the observation that exposure to insulin increases GH receptors on rat hepatocytes in vitro. But modest insulin deficiency can be associated with low serum IGF-I in the absence of any change in the hepatic GH binding, suggesting that insulin also controls IGF-I directly. In primary cultures of hepatocytes, insulin stimulates the transcription of IGF-I gene, even in the absence of GH. 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 triiodothyronine (T3) in fasted individuals. It is possible, however, that the major effect of thyroid hormones on IGF-I synthesis is exerted in the pituitary, where thyroid hormones positively regulate GH gene expression. In vivo and in vitro studies, however, show that thyroid hormones potentiate hepatic IGF-I synthesis in response to GH. Up-regulation of hepatic GH binding by thyroid hormones may mediate this potentiation of GH-induced IGF-I synthesis. Indeed, thyroid hormones increase GH receptor and its gene expression in hepatocytes. Treatment of fasted rats with T3 seems to prevent partially the decline in pituitary GH mRNA levels and serum IGF-I concentrations.

**Role of Nutrients**

Because of the close relationship between protein intake and serum insulin concentrations, it has been difficult to determine whether the reduced IGF-I in protein-restricted rats is related directly to low insulin or to decreased availability of amino acids. In rats made diabetic with streptozotocin, treated with insulin, and then submitted to a low- or normal-protein diet, the diet-induced decline in IGF-I persists despite high circulating insulin (two to three times normal values) (Figure 2). This suggests that dietary protein restriction decreases serum IGF-I independent of insulin and that protein restriction (and perhaps decreased availability of specific amino acids) may be more important mechanistically than serum insulin concentrations. In primary cultures of rat hepatocytes, amino acid deprivation causes a rapid and progressive decline in IGF-I mRNA levels, whereas amino acid excess causes an increase (Figure 3). Among the amino acids, tryptophan seems to be the most critical in the regulation of IGF-I, as its removal from the medium for 48 hours causes a dramatic decline in IGF-I mRNA and IGF-I release. Across a broad range of amino acid concentrations, both insulin and GH raise IGF-I mRNA levels in proportion to the amino acids.
Serum IGF-I and Serum insulin

Figure 2. Role of insulin in the control of serum IGF-I in protein-restricted rats. Rats were made diabetic with streptozotocin, treated with insulin, and then submitted to a low- or normal-protein diet (5% versus 15% protein). Double asterisk (**) corresponds with p < 0.01 compared with diet-matched controls. In normal-fed diabetic rats, insulin treatment restores serum IGF-I to normal. In contrast, in protein-restricted diabetic rats treated with insulin, serum IGF-I remains low. Reproduced from Thissen et al.,53 with permission from John Libbey Eurotext.

Acid concentration. In parallel to the stimulation of IGF-I, amino acid excess inhibits the expression and release of IGFBP-1, a binding protein considered to inhibit actions of IGFBP-1.21 In particular, leucine limitation strongly induces IGFBP-1.22 Taken together, these observations suggest that GH, insulin, and amino acids can regulate hepatic production of IGF-I independently. Each of these controls IGF-I synthesis at least by acting at the transcriptional level.23 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. In the case of zinc, depletion for 24 hours in rat hepatocytes by using a specific chelator does not cause IGF-I gene expression to decline, despite the clear inhibition of the metallothionein mRNA.24

Role of Changes in IGF-1 Gene Expression

Decreased serum IGF-I in dietary restriction correlates with reduced steady-state levels of hepatic IGF-I mRNA,25 suggesting that nutritional regulation of IGF-I gene expression takes place at a pretranslational level. Results of nuclear run-off and nuclear transcript abundance studies propose that the fasting-related decline in IGF-I mRNA levels might be caused by a decrease in the rate transcription of the IGF-I gene.26 The decrease in cytoplasmic IGF-I mRNA levels caused by fasting may result also from a diminished splicing of IGF-I pre-mRNAs, thereby attenuating the maturation of the primary transcript.27 In contrast to fasting, the decline of liver IGF-I mRNA in protein-restricted rats is thought to result predominantly from a posttranscriptional mechanism. Supporting this interpretation is the observation that protein-restricted rats retain the ability to muster normal IGF-I mRNA responses to high doses of exogenous GH. This indicates that the transcriptional machinery is intact.28 Furthermore, the faster decline of the 7.5 kb IGF-I mRNA transcript after a single injection of GH in protein-restricted rats compared with normally fed rats supports the idea that protein restriction causes decreased stability of liver IGF-I mRNA. The 7.5 kb mRNA transcript differs from the other species of mRNA by a long 3' untranslated region that contains several ad- enine uracil (AU)-rich sequences. Such sequences are known to be involved in other genes in the regulation of the stability and/or translation of the mRNA. Indeed, in primary cultured rat hepatocytes, reduction of amino acid

Figure 3. Interaction between GH and amino acid availability in the regulation of IGF-I mRNA levels in cultured rat hepatocytes. IGF-I mRNA levels were assessed in hepatocytes cultured for 24 hours in three media differing in their amino acid concentrations (0.2x, 1x, and 5x the normal rat arterial plasma amino acid concentration) with or without GH (500 ng/mL). Reproduced from Thissen et al.,23 with permission from The Endocrine Society.
availability results in decreased stability of the IGF-I mRNA 7.5 kb transcript. Therefore, it appears likely that the decrease in steady-state IGF-I mRNA in protein-restricted rats owes primarily to posttranscriptional events.

Regulation of IGF-I synthesis by nutrients also may be under translational control, but possible mechanisms responsible for this are not known. It appears, however, that all IGF-I mRNA size-classes associate with polysomes, even in the liver of protein-restricted rats, suggesting that they have the capacity to engage in IGF-I synthesis. Also, using in vitro translation techniques, no obvious impairment of translation of IGF-I peptide results from fasting.

Mechanisms Involved in the Nutritional Regulation of IGF-I Action

Role of IGFBPs

The IGFBPs are believed to exert both stimulatory and inhibitory effects on IGF-I actions, but the mechanisms involved are still speculative. Among the proposed functions of the IGFBPs are the prolongation of the plasma half-life of IGF-I, the control of the rate of IGF-I transport from the vascular compartment, and the regulation of the interaction between IGF-I and the type-I IGF receptor on the cell surface. IGF-I bioavailability may be controlled by posttranslational modifications of IGFBPs (partial proteolytic degradation by specific IGFBP proteases, selective dephosphorylation) resulting in IGFBPs with reduced affinity for IGF-I. Less than 5% of the IGF-I in the circulation is free peptide, and most (>90%) is bound in the 150 kDa complex, which consists of IGF-I, IGFBP-3, and an ALS. This complex, which is believed not to cross the capillary endothelium and which has a relatively long half-life (3–6 hours in rats and 12–15 hours in humans), probably serves as a storage pool for IGF-I. The remainder of the IGF-I in the circulation is bound to small IGFBPs (IGFBP-1, -2, or -4), forming complexes of 30–40 kDa that can cross the capillary endothelium. These latter IGFBPs may be involved in the delivery of IGF-I to tissues.

Dietary manipulations change the abundance of serum IGFBPs in humans and animals. In general, dietary restriction decreases serum IGFBP-3 concentrations while it increases serum IGFBP-1 and IGFBP-2. Changes in IGFBP-1 are very rapid, whereas changes in IGFBP-2 and IGFBP-3 take several days. Most of the alterations in levels of IGFBPs result from parallel changes in their liver gene expression.

The nutritional regulation of IGFBPs is exerted by both hormones and nutrients. The decline of IGFBP-3 in protein-restricted rats seems to be related to the decreased serum IGF-I itself, because IGF-I infusion in protein-restricted rats normalizes serum IGFBP-3. The decline of serum IGFBP-1 caused by nutrient intake results mainly from an increase in insulin, glucose, and amino acid concentrations.

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. Indeed, plasma IGF-I clearance is accelerated in situations characterized by a decrease or absence of serum IGFBP-3 (e.g., hypophysectomized or pregnant rats). By following the decline of radioactivity in the circulation of rats injected with a bolus of [125I]-labeled IGF-I, Thissen et al. showed that the clearance of [125I]-IGF-I is increased by 50% in protein-restricted rats (Figure 4). This acceleration of clearance of IGF-I owes to a more rapid distribution of IGF-I into the tissues (shorter t1/2m) and not to a change in the elimination half-life (t1/2e). In the normal-fed rats, IGF-I was almost equally distributed between the 150 kDa and the 30 kDa binding protein complexes, whereas in protein-restricted rats, IGF-I was preferentially bound to IGFBPs in the small (30 kDa) complex, as evaluated by size exclusion high-performance liquid chromatography (HPLC) of serum samples. Because the small IGFBP complex is believed to facilitate the transport of IGF-I from serum to tissues, the preferential association of IGF-I with these IGFBPs in malnourished animals might allow a faster transcapillary passage and distribution to tissues.

Role of the Sensitivity to IGF-I

Several observations suggest that dietary restriction can impair the growth-promoting actions of IGF-I. When protein-restricted or zinc-deficient rats are infused with re-
combinant IGF-I by osmotic minipump for a week, carcass growth (body weight and tibia epiphyseal plate) is not stimulated despite the normalization of serum IGF-I. By contrast, growth of the spleen and kidney is enhanced. These results suggest that, in addition to its effects on IGF-I gene expression and IGF binding proteins, protein or zinc restriction causes organ-specific resistance to the growth-promoting properties of exogenous IGF-I. This observation supports the idea that nutrient insufficiency can block the growth-promoting properties of IGF-I while some other properties of IGF-I are unaffected or are less affected by dietary restriction. The fact that nutrients can control the response to IGF-I directly has been demonstrated in fibroblast cultures where zinc depletion inhibits the mitogenic action of IGF-I.

Evidence for the Regulation of IGF-I in Catabolic States

Decline of IGF-I and Changes in IGFBPs

Critical illness is associated with low circulating concentrations of IGF-I, IGFBP-3, and the ALS. These three polypeptides are normally upregulated by GH, and together form a 150 kDa complex, the principal form of circulating IGF-I. The most marked alteration in the IGF system seems to be a dramatic increase in the activity of circulating IGFBP-3 protease, contributing to the decline in IGFBP-3 and to the shortening of the half-life of IGF-I in serum. These changes seem to be related to the risk of mortality of critically ill patients because survival is associated with higher IGF-I and IGFBP-3 concentrations and lower protease activity. The extent of the injury (e.g., total body surface area burn) is reportedly correlated inversely with the IGF-I concentrations. Unlike IGFBP-3, small IGFBPs such as IGFBP-1 and IGFBP-2 are usually elevated in the circulation of critically ill patients. The role of the decrease in IGF-I in the critical illness is still disputed. Decreased IGF-I concentrations may be responsible for producing and prolonging the catabolic reaction.

Alterations of GH Secretion and GH Responsiveness in Critical Illness

Critically ill patients show augmented GH concentration levels in the circulation with reduced oscillatory activity. The rise in GH, together with the decrease in circulating IGF-I, indicates a relative resistance to the action of GH. The presence of GH resistance is supported by several studies in septic patients in which exogenous GH fails to attenuate nitrogen losses and to stimulate IGF-I. This is compatible with an adaptive change of GH action away from the indirect anabolic effects mediated by IGF-I toward the direct effects responsible for the increased availability of energy substrates. It is possible, therefore, that the large amount of released GH still exerts direct effects on nutrient mobilization in an attempt to provide essential substrates for survival. Such changes are likely to be beneficial to the acute fasting sick patient by providing fuels. They may, however, be counterproductive in the setting of modern intensive care where patients can be fed for prolonged periods of time. The increase in GH secretion persists despite the calorie and protein supply afforded by artificial feeding, indicating that nutrient deprivation is usually not responsible for the GH resistance observed in these patients. High cortisol levels and insulin resistance have been proposed to contribute to this GH resistance. Partial GH resistance may be overcome, however, by increasing the dose of exogenous GH. Indeed, many studies have reported beneficial effects of exogenous GH on nitrogen balance and serum IGF-I in patients who are postoperative or who have burns, trauma, or sepsis. GH secretion is reduced when critical illness is prolonged, in contrast to acute critical illness. In chronic critical illness, low GH levels are correlated with low levels of IGF-I, IGFBP-3, and ALS, suggesting that the decrease of the three components of the 150 kDa circulating complex is the result of the reduced GH secretion. This hypothesis is supported by the clear response of the whole somatotrope axis to GH secretagogues in the chronic phase of critical illness. This is in contrast to observations made in the acute setting, where decreased IGF-I is thought to be primarily the consequence of GH resistance.

Mechanisms of the Regulation of IGF-I During Sepsis

Endotoxin (Escherichia coli lipopolysaccharide [LPS]) is a component of the gram-negative bacterial wall that is believed to mediate many of the consequences of infection. Injection of endotoxin in rats produces a rapid, major, sustained decrease in circulating IGF-I concentrations. This model of acute endotoxemia has been used to investigate the mechanisms involved in the decrease of IGF-I in response to sepsis.

Role of GH Secretion

In the rat, stressful stimuli, including LPS injection, result in a marked acute decrease in plasma GH. This suppression of GH secretion is mediated at least in part by interleukin (IL)-1β, which acts to stimulate SRIH directly and probably to inhibit GHRH through increased corticotrophin-releasing hormone. GH injection, however, does not reverse the endotoxin-induced reduction of serum IGF-I. Unlike rats, humans have increased GH secretion in response to acute stress. Despite increased GH secretion, serum IGF-I is also reduced, suggesting that mechanisms for IGF-I production by tissues are insensitive to GH in catabolic humans, as in rats. This suggests that impaired GH secretion is not responsible for decreased serum IGF-I concentrations in patients having acute criti-
cal illness. In contrast, GH secretion is reduced in prolonged critical illness. The mechanisms responsible for decreased GH secretion in response to chronic stressful situations in humans are less clear. A possible deficiency in endogenous GH-releasing peptide together with a reduced SRIH tone and maintenance of some GHRH effect has been suggested to explain both reduced spontaneous GH secretion and pronounced responsiveness to GH secretagogues.41

**Role of GH Receptor**

To unravel the mechanisms of LPS-induced GH resistance in rats, Defalque et al.42 investigated whether liver GH binding sites might be decreased in response to endotoxin. The data showed liver GH binding and GHR mRNA are markedly reduced 10 hours after LPS injection (Figure 5).42 Although this dramatic decrease of GH binding is similar in amplitude to changes observed during fasting, the kinetics of the decrease is much faster in response to LPS than to fasting. The marked reduction in GH binding after LPS contrasts strongly with the modest decrease in GHBP levels. The reason for this discrepancy may reside in the longer half-life of the serum GHBP (2.4 hours) compared with the liver GHR (30–40 minutes).

**Role of Cytokines**

The pro-inflammatory cytokines IL-1β and tumor necrosis factor (TNF-α), which are released in response to LPS, are believed to play a role in the catabolic reaction caused by sepsis. The actions of these cytokines on muscle metabolism appear to be indirect because they are ineffective when incubated in vitro with skeletal muscle. Fan et al.41 have shown that the endotoxin-induced decrease in circulating IGF-I is mediated mainly by enhanced endog-

Figure 5. Liver GH-binding sites 5 and 10 hours after administration of LPS at two different doses (250 and 750 μg/100 g body weight). Double asterisk (**) corresponds with \( p < 0.01 \) and triple asterisk (***), corresponds with \( p < 0.001 \) compared with time-matched controls. Reproduced from Defalque et al.,42 with permission from The American Physiological Society.

Figure 6. IGF-I mRNA response to increasing concentrations of GH in primary cultures of rat hepatocytes incubated in presence (+) or absence (-) of interleukin (IL)-1β (10 ng/mL). Triple asterisk (***), corresponds with \( p < 0.001 \) compared with the corresponding group without IL-1β. Reproduced from Thissen and Verniers,45 with permission from The Endocrine Society.

**Role of Glucocorticoids**

The adrenocorticotroph axis is activated in critical illness and glucocorticoids can accelerate muscle proteolysis in sepsis. Evidence shows that glucocorticoids interfere with the function of the somatotrope axis. In vivo studies have shown that glucocorticoids antagonize the GH-induced increase in IGF-I mRNA in the liver of hypophysectomized rats. To elucidate the mechanisms whereby glucocorticoids may alter liver GH responsiveness, Beauloye et al. investigated the effect of dexamethasone on the IGF-I mRNA response to GH and on the expression of the GH receptor gene in primary cultures of rat hepatocytes. These results show that excess glucocorticoids attenuate the IGF-I mRNA response to GH and strongly inhibit GHR

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expression. Moreover, increased glucocorticoids may be involved in the decrease of IGF-I in sepsis, because pre-treatment of rats with the glucocorticoid receptor antagonist RU-486 prevents the IL-1β-induced decrease in plasma IGF-I concentrations and liver IGF-I mRNA.47

**Role of Changes in IGF-I Production and Clearance**

The sepsis-induced decrease in circulating IGF-I is attributed primarily to a reduction in hepatic production. In infected dogs, the net hepatic release of IGF-I is decreased. This is accompanied by a decrease in liver IGF-I gene expression after endotoxin injection.47 Pharmacokinetic analysis of blood [125I]-IGF-I decay curves indicates that the half-time for whole body clearance of [125I]-IGF-I from the circulation is not altered by LPS. However, LPS increases uptake of [125I]-IGF-I by the spleen, liver, lung, and kidney while decreasing uptake by the pancreas and the gastrointestinal tract.49

**Role of the Sensitivity to IGF-I**

Evidence suggests the anabolic actions of IGF-I on muscle protein synthesis may be impaired during catabolism in which cytokines are overexpressed. When myoblasts are exposed to TNF-α, the stimulation of protein synthesis by IGF-I or serum is severely blunted. The fact that TNF-α does not inhibit IGF-I-stimulated thymidine uptake suggests that this cytokine acts specifically on a component of the IGF-I signal transduction involved in stimulating protein synthesis.49 Similar effects have been reported in fibroblasts in which the production of collagen by IGF-I is suppressed by TNF-α and interferon-γ.50 These data are in contrast with the observation that IGF-I can still enhance the rate of protein synthesis in muscle of septic rats. However, in this last report, the amplitude of the anabolic response to IGF-I in septic muscle might be attenuated by comparison with that observed in normal muscle.51

**Conclusions**

Both starvation and sepsis are characterized by GH insensitivity, which leads to a reduction in circulating IGF-I, a major growth factor. The mechanisms leading to impaired GH responsiveness in both situations differ in several aspects. The decline of circulating IGF-I in these situations may contribute to the loss of body cell mass. The regulation of IGF-I by nutrients and cytokines links nutrition, inflammation, and anabolic drive and brings an interface among nutrients, hormones, and cytokines, which all act in concert to control anabolism and growth.52

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