Nutritional Regulation of Insulin-Like Growth Factor-I

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Several lines of evidence indicate that in the human, insulin-like growth factor-I (IGF-I) is nutritionally regulated. Both energy and protein availability are required for maintenance of IGF-I. Measurements of serum IGF-I constitute a sensitive means for monitoring the response of acutely ill patients to nutritional intervention. Serum IGF-I may also serve as a marker for evaluation of nutritional status. Our findings and those of others in animal models suggest that nutrients influence synthesis and action of IGF-I and its binding proteins (IGFBPs) at multiple levels. In fasting, liver growth hormone (GH) binding is decreased, providing one explanation for decreased IGF-I. In protein restriction, GH receptors are maintained, but there is evidence for a postreceptor defects. The latter results from pretranslational and translational defects. Amino acid availability to the hepatocytes is essential for IGF-I gene expression. Protein malnutrition not only decreases IGF-I production rate, but also enhances its serum clearance and degradation. Finally, there is evidence for selective organ resistance to the growth-promoting effects of IGF-I in protein-restricted rats.

GROWTH IS A COMPLEX process governed by many hormonal interactions. It is also dependent on adequate nutrient intake. Among the many hormones involved in the growth process, growth hormone (GH) plays a central role. In the circulation, GH is bound in part to a GH-binding protein (GHBP) that corresponds to the extracellular portion of the GH receptor.[1] GH exerts many of its growth-promoting actions indirectly by binding to specific receptors in many tissues and stimulating the production of insulin-like growth factor-I (IGF-I).[2] Previously referred to as somatomedin-C, IGF-I is a single-chain polypeptide composed of 67 amino acid residues and structurally related to proinsulin.[3-5] IGF-I is produced in most organs, but the liver is the major source of the circulating peptide.[6-10] The highest concentrations of IGF-I are found in blood.[11] IGF-I promotes the growth of most cell types and, together with other growth factors, induces cellular differentiation and differentiated functions of specialized cells.[12,13] The biological effects of IGF-I are mediated by specific high-affinity receptors (type I IGF receptors) that have structural homology with the insulin receptor. The ubiquity of sites of IGF-I production and of its receptor has led to the concept that it acts by autocrine/paracrine mechanisms in addition to a classic endocrine action.[14-16]

In serum and most body fluids, IGF-I is bound to high-affinity binding proteins (IGFBPs). Most IGF-I circulates as a 150-kd complex consisting of IGF-I, IGFBP-3 (47 to 53 kd), and an acid-labile subunit (84 to 86 kd). The remainder of bound IGF-I circulates as a 30- to 40-kd complex (IGF-I bound to IGFBP-1, -2, or -4). Each of these binding proteins is regulated differently, and each is believed to perform different functions.[17-21]

The major hormonal regulator of circulating IGF-I is GH.[22] Serum IGF-I levels reflect GH status, being low in GH-deficient children and elevated in patients with acromegaly. Insulin also plays a role in regulation of IGF-I. In growth retardation associated with poorly controlled diabetes (Mauriac's syndrome), serum IGF-I concentrations are reduced despite elevated GH levels.[23] Studies in rats made diabetic with streptozotocin have shown that the GH resistance that occurs in insulinopenic animals is due to a GH postreceptor defect.[24,25]

Based on clinical observations and experimental data from animals, the concept has emerged that food intake and nutritional status play an important role in the control of IGF-I. In this article, we will summarize the data on nutritional control of IGF-I in the human. We will then review our experimental studies on the mechanisms by which nutrients control both the production and anabolic actions of IGF-I.

CONTROL OF IGF-I BY NUTRIENTS: CLINICAL STUDIES

Food intake and nutritional status are major regulators of IGF-I. Thus, chronic undernutrition leads to reduced serum IGF-I. Early studies have shown that bioactive somatomedin in serum is decreased in children with kwashiorkor, and this reduction is accompanied by decreased serum albumin.[26,27] Reports from Hintz et al[27] and Smith et al[28] indicate that low somatomedin bioactivity is also present in children with marasmus, but is independent of changes in serum albumin. Studies using radioimmunoassays also indicate that serum IGF-I is reduced in patients with protein-calorie malnutrition.[29] Decreased serum IGF-I values are not restricted to classic forms of malnutrition, since conditions such as anorexia nervosa, severe inflammatory bowel disease, or celiac disease are often associated with reduced serum IGF-I. In general, the magnitude of IGF-I reduction relates to the severity of the nutritional insult, and IGF-I levels consistently increase with nutritional rehabilitation.[30-32] In human immunodeficiency virus–infected patients, a decline of serum IGF-I is also present and correlates with serum albumin and body-cell mass.[33]

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In adults, IGF-I values decline within 24 hours of the start of fasting, reach 10% to 15% of prefast values by 10 days, and promptly return toward normal with refeeding. Changes in nitrogen balance parallel changes in IGF-I.[34] Serum IGF-I concentrations appear to be a good indicator of directional changes in nitrogen balance.[35] Both energy and protein are important in regulation of IGF-I because each is essential for restoration of serum IGF-I after fasting.[35] A threshold amount of energy (~ 12 kcal/kg/24 h) is essential for IGF-I recovery after fasting, and the quality of dietary protein (content of essential amino acids) also regulates IGF-I.[36,37]

Serum IGF-I measurements may offer a more sensitive index of short-term changes in nutritional status than other markers. Indeed, in malnourished adults receiving nutritional support for 10 to 16 days, serum IGF-I increases rapidly, while serum transferrin, prealbumin, or retinol-binding protein exhibit only minimal changes.[38] Therefore, IGF-I appears to be a clinically useful indicator of nutritional status. Unterman et al[39] reported that serum IGF-I is effectively reduced to a mean of 38% of control values in 31 hospitalized malnourished patients. Furthermore, IGF-I values were more informative than anthropometric and classic laboratory indices of nutritional status. However, other studies reporting on the use of IGF-I measurement to screen for malnutrition in large groups of normal individuals have shown no positive correlation between serum IGF-I and dietary intake or anthropometric indices.[40,41] This may be due in part to the low prevalence of malnourished subjects in the study group. Sullivan and Carter[42] have shown recently that serum IGF-I may be a clinically useful marker for protein-energy undernutrition among metabolically stable, hospitalized elderly patients. Furthermore, in these patients, low IGF-I levels appeared as a strong predictor of life-threatening complications.

Inversely, excessive food intake may cause a small stimulation of serum IGF-I. Thus, overfeeding a normal-weight woman (1,200 to 1,600 kcal/d) caused a 19% increase of serum IGF-I by day 14.[43] In contrast, in obesity serum IGF-I concentrations are moderately decreased and correlate negatively with the abdominal fat mass.[44,45] This may be due in part to the reduced GH levels in obese subjects.

MALNUTRITION AND GH RESISTANCE

In severe protein restriction (kwashiorkor) or protein-energy deprivation (marasmus), growth retardation is associated with low serum IGF-I levels, despite elevated or normal GH serum concentrations.[26,27,29] In man, the decrease of IGF-I during fasting is associated with elevated serum GH.[46] Moreover, the IGF-I response to GH is blunted in GH-deficient patients subjected to fasting.[47] In rats in which serum somatomedin (IGF) is reduced by fasting, pharmacological doses of GH fail to increase somatomedin activity.[48] Taken together, these data indicate that restriction in food intake leads to GH resistance.

ROLE OF GH RECEPTOR AND POSTRECEPTOR DEFECTS

The hypothesis was tested that the GH resistance in fasting results from a loss of GH receptors.[49-52] To this end, 6-week-old female rats were fasted for 3 days and then refed a standard diet. After 1 and 3 days of fasting, serum IGF-I had declined by 68% and 87%, respectively[49,50] (Fig 1). After 4 days of refeeding, IGF-I had returned to the initial prefast values. These changes in IGF-I were paralleled by changes in the number of hepatic GH-binding sites, determined with [^{125}I]-labeled bovine GH. However, there were no changes in the affinity constants of the binding. Further studies by Straus and Takemoto[53] showed that GH receptor mRNA abundance in the liver also declines during fasting and responds to refeeding. In fasted rats, circulating GHBP was decreased in parallel with liver GH receptors and serum IGF-I. In humans also, GHBP levels decrease in parallel with serum IGF-I concentrations during severe undernutrition, such as anorexia nervosa.[31] This suggests that in humans also, reduced liver GH-binding capacity may impair GH responsiveness during extreme dietary restriction.

In protein-restricted rats, the role of liver GH receptors in the decline of serum IGF-I is more questionable than in fasting. We have observed that during the first 12 and 24 hours of protein restriction in prepubertal rats, serum IGF-I was decreased by 58% and 66%, respectively, whereas liver GH binding was reduced by only 15% to 20%. Administration of rat GH did not prevent the effects of protein restriction on serum IGF-I.[54] In 3- to 4-week-old prepubertal rats, feeding a low-protein diet (5% casein) for 1 week caused an 80% to 90% reduction in serum IGF-I as compared with levels in control rats fed 15% casein. At the same time, GH binding by liver was either unchanged (3-week-old rats) or decreased by only 30% to 40% (4-week-old rats).[55] The slight decrease of liver somatogenic receptors after 1 week of a low-protein diet could be prevented by continuous infusion of GH. In contrast, in these GH-

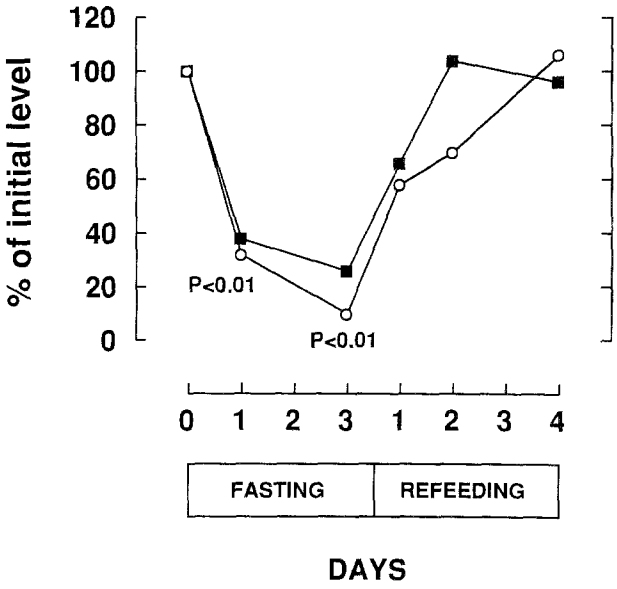

Fig 1. Effect of fasting and refeeding on rat serum IGF-I (○) and liver GH-binding sites (■). Data are expressed as the mean value for controls on the first day of the study (day 0). Reproduced by permission of the J. Endocrinol Ltd, after adaptation.[49]

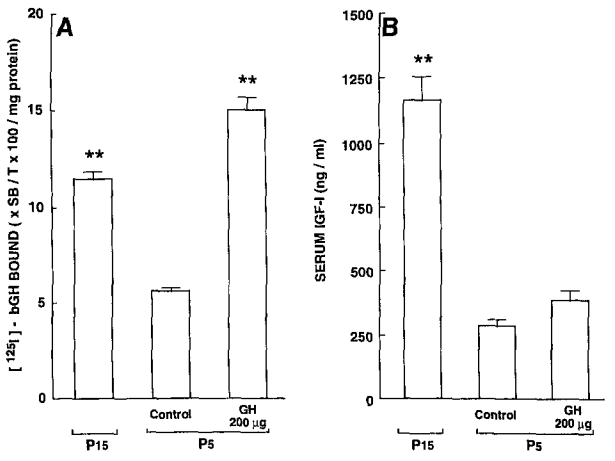

Fig 2. Effect of 1 week of dietary protein restriction ([P5] 5% protein diet) on liver GH-binding sites (A) and serum IGF-I concentrations (B) in 4-week-old rats. P5 rats were either untreated (control) or infused for 1 week with rat GH 200 µg/d using an osmotic minipump (P5 GH 200 µg). The P15 group received a normal-protein diet (15% protein). Total liver GH-binding sites were determined on liver homogenates treated with 4 mol/L $MgCl_2$ to remove the endogenous bound hormone. **P < .01 v P5 control group. bGH, bovine GH; SB, specifically bound radioactivity; T, total radioactivity. Reprinted with permission.[56] © The Endocrine Society.

treated animals, IGF-I remained low despite normal liver GH-binding capacity and elevated GH levels[56] (Fig 2). The possibility of a postreceptor defect was evaluated by comparing the serum IGF-I response of protein-restricted, hypophysectomized rats with that of normal-fed rats following a single injection of GH. In normal-fed animals, bovine GH produced a dose-dependent increase in serum IGF-I, whereas in rats fed a low-protein diet, the IGF-I response to bovine GH was severely blunted despite normal liver GH binding.[57] Finally, studies performed on hepatocytes isolated from 8-week-old, protein-restricted rats showed that reduced IGF-I occurred in the presence of normal numbers of GH receptors on the surface of the cells.[58] We therefore conclude that the GH resistance in protein restriction is due primarily to defects distal to the binding of GH with its receptor.

ROLE OF INSULIN AND AMINO ACID AVAILABILITY

Insulin levels are reduced by ingestion of a low-protein diet. We therefore investigated whether this factor may play a role in the reduction of IGF-I during dietary protein restriction. Using a model of rats made diabetic with streptozotocin, treated with insulin, and then submitted to a low- or normal-protein diet, we observed that dietary protein restriction exerts its effects on IGF-I independently of insulin[59] (Fig 3). Thus, protein restriction by itself is the major cause of reduced serum IGF-I in this model. Support for a primary role of amino acid availability in the control of IGF-I gene expression has been obtained in primary cultures of rat hepatocytes.[60] When the hepatocytes are incubated with a medium containing only 20% of the amino acid concentration of normal serum, IGF-I mRNA abundance decreases to 56% of control values after 24 hours; controls are cells incubated with a medium containing normal amino acid concentrations. Other reports have suggested a major role of tryptophan in the maintenance of IGF-I mRNA in hepatocytes in culture.[61,62]

MOLECULAR MECHANISMS INVOLVED IN THE GH POSTRECEPTOR DEFECT CAUSED BY PROTEIN RESTRICTION

We have investigated whether pretranslational and/or translational defects might contribute to the nutritionally induced decrease in serum IGF-I. To this end, we determined by Northern blot analysis the IGF-I mRNA levels in liver tissue of prepubertal rats fed a low-protein (5% casein) or normal-protein (15% casein) isocaloric diet for 1 week. Dietary protein restriction resulted in a 40% to 60% decrease in the abundance of all IGF-I mRNA transcripts (7.5, 4.7, 1.5 to 1.9, and 0.9 to 1.2 kb) in comparison to the abundance in normal-fed rats. The 7.5-kb transcript showed a tendency to be reduced more than other transcripts[63] (Fig 4). Reduced liver IGF-I mRNA together with low serum IGF-I levels have also been observed in fasting or neonatal food restriction.[53,64-66] Protein restriction or fasting also cause reduction in IGF-I mRNA in nonhepatic tissues such as kidney, muscle, gut, and brain.[67,68] Some studies suggest that nutritional intake may regulate the rate of IGF-I gene

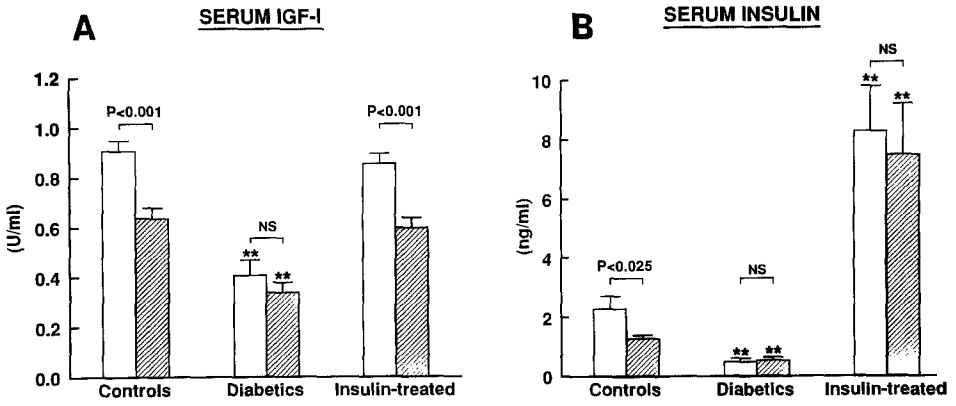

Fig 3. Serum IGF-I (A) and insulin (B) concentrations in 42-day-old control rats, rats made diabetic with streptozotocin, and diabetic rats treated with insulin. In each experimental group, rats were fed the normal-protein diet (15% protein, □) or, for 1 week before killing, a low-protein diet (5% protein, ▨). Adapted with permission.[59] © The Endocrine Society.

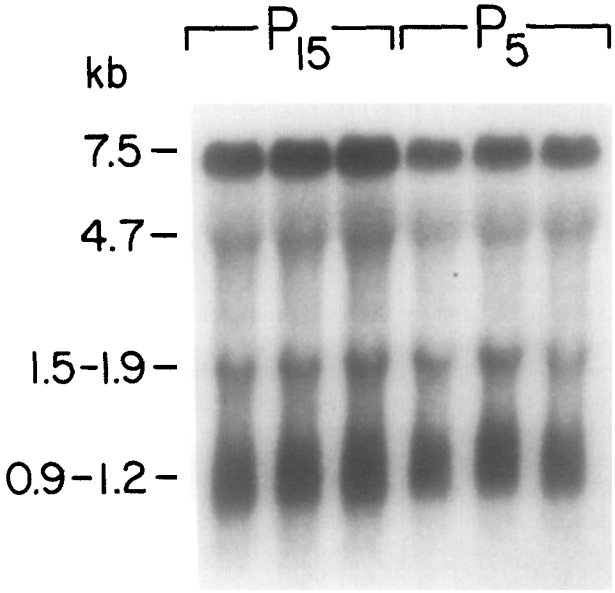

Fig 4. Northern blot analysis of liver IGF-I mRNA in 3 normally fed (P15) and 3 protein-restricted (P5) 4-week-old rats. Protein-restricted diet was given for 1 week. Samples of liver RNA (20 μg) were loaded in each well. The blot was hybridized with a rat exon 3–specific IGF-I RNA probe. The signal obtained with hybridizing by a chicken β-actin cDNA probe was equivalent in both groups.

transcription, but it is possible that increased mRNA instability is also a mechanism for decreased mRNA levels.

We also investigated the effects of exogenous GH administration on liver IGF-I mRNA levels in prepubertal protein-restricted rats. We found that high doses of GH normalized liver IGF-I mRNA but not liver or serum IGF-I concentrations.[63] Another series of experiments were conducted to determine the effects of protein deprivation on the IGF-I gene response to acute exposure to GH. Prepubertal hypophysectomized rats were subjected to a low- or normal-protein diet for 1 week, and were thereafter injected with a single dose of rat GH. Liver IGF-I mRNA levels were determined at various time intervals together with serum IGF-I levels. GH injection produced a comparable surge of liver IGF-I mRNA in both dietary groups, but failed to increase serum IGF-I normally in the group fed low levels of protein[63] (Figs 5 and 6). These data show that the machinery involved in transcription of the liver IGF-I gene is intact in protein-restricted rats, because these animals retain the ability to muster normal IGF-I mRNA responses to high doses of exogenous GH. Furthermore, the discrepancy between normal liver IGF-I mRNA abundance and low serum and liver IGF-I peptide concentrations suggests that translational stalling of IGF-I mRNA is at least partially involved in the low serum IGF-I concentrations

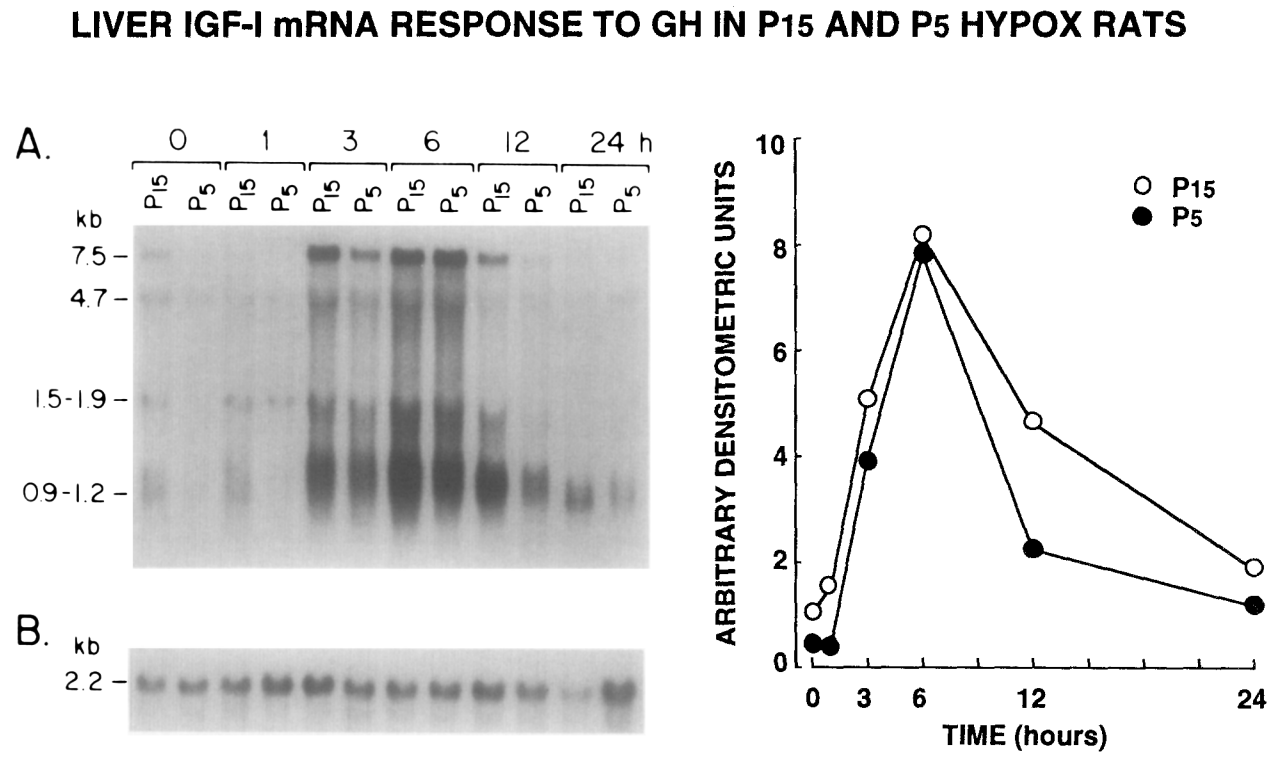

Fig 5. (A and B) Northern blot analysis of liver IGF-I mRNA in protein-restricted (P5) and normally fed (P15) hypophysectomized rats at increasing times after a single GH injection (rat GH 200 μg/100 g body weight at time 0). Each lane represents mRNA from a liver pool of 3 to 6 rats. Samples of liver poly(A)$^+$ RNA (10 μg) were loaded in each well. The blot was hybridized with a rat exon 3–specific IGF-I RNA probe (A) or a chicken β-actin cDNA probe (B). (C) Time course of total IGF-I mRNA in protein-restricted (●) and normally fed (○) hypophysectomized rats after a single GH injection. Each value represents the mean of 6 different blots run with a single RNA preparation from a liver pool, and is expressed in arbitrary densitometric units by assigning hepatic RNA pooled from untreated P15 rats a value of 1. Reprinted with permission.[63] © The Endocrine Society.

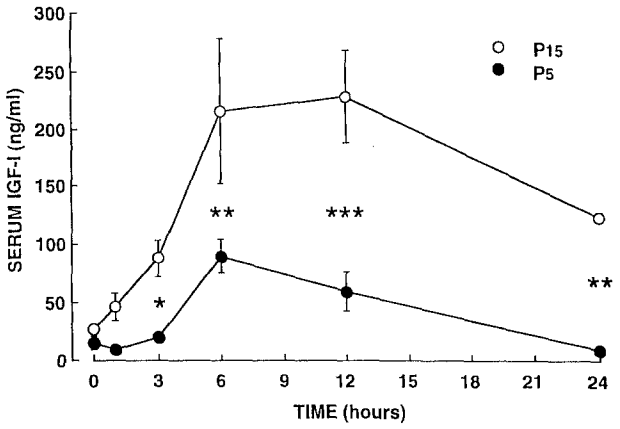

Fig 6. Serum IGF-I concentrations in protein-restricted (●) and normally fed (○) hypophysectomized rats after a single GH injection (rat GH 200 μg/100 g body weight). Each value represents the mean ± SEM of 3 to 6 rats. *P < .05, **P < .01, ***P < .001. Reprinted with permission.[63] The Endocrine Society.

during dietary protein restriction. Studies on the nature of this translational defect show that dietary protein restriction does not affect binding of IGF-I mRNA to polysomes, one of the mechanisms involved in initiation of IGF-I mRNA translation.[69]

EFFECTS OF PROTEIN RESTRICTION ON SERUM CLEARANCE AND DEGRADATION OF IGF-I

The effects of protein restriction on serum IGF-I clearance and degradation were measured after a bolus injection of [^{125}I]-labeled IGF-I.[70] Protein restriction accelerated the rate of serum clearance of IGF-I, as well as the rate of peptide degradation. This could be explained by the fact that in protein-restricted rats, IGF-I binds preferentially to the 40-kd IGFBP complex, which has a shorter half-life than the 150-kd complex. It was also found that endogenous IGF-I production, calculated from serum levels and clearance data, was reduced by 29% during protein restriction. This was consistent with the previous experiments showing reduced IGF-I mRNA liver content, translational stalling, and low tissue and serum IGF-I levels in protein-restricted rats.

EFFECTS OF DIETARY PROTEIN RESTRICTION ON THE GROWTH-PROMOTING ACTIONS OF IGF-I

We evaluated whether dietary protein restriction in prepubertal rats could impair the anabolic actions of IGF-I. Four-week-old rats fed a low-protein diet (5% casein) were infused with recombinant human IGF-I (300 μg/d) or rat GH (200 μg/100 g body weight/d) by osmotic minipump for 1 week.[71] Despite normalization of serum IGF-I by IGF-I infusion, carcass growth was not stimulated (Fig 7). In contrast, growth of the spleen and kidney was enhanced (+45% and +28%, respectively). Serum IGFBP-3 is decreased by 34% in protein-restricted animals, and is restored to normal by IGF-I infusion. Contrary to the selective effects of IGF-I on the growth of protein-restricted rats, well-nourished hypophysectomized rats infused with recombinant human IGF-I (150 μg/d) showed a significant growth response, including carcass and organ growth and normalization of IGFBP-3 values. The latter indicates that our IGF-I preparation and mode of delivery were effective. In further experiments, protein-restricted rats received a combined infusion of IGF-I and GH. Even in this condition, no stimulation of carcass growth was observed.[72] These results agree with the report by Philipps et al[73] showing that protein-energy deprivation in neonatal rats blocks IGF-I effects on somatic growth. Other observations showed that the body weight loss caused by fasting can be partially blunted by IGF-I treatment in animals.[74,75] The difference of the severity between the two nutritional insults (malnutrition *v* fasting), specifically considering body weight loss and intensity of the catabolism, might explain the divergence of the results. We conclude from these studies that (1) dietary protein restriction causes relative, organ-specific resistance to the growth-promoting properties of exogenous IGF-I, and this resistance might

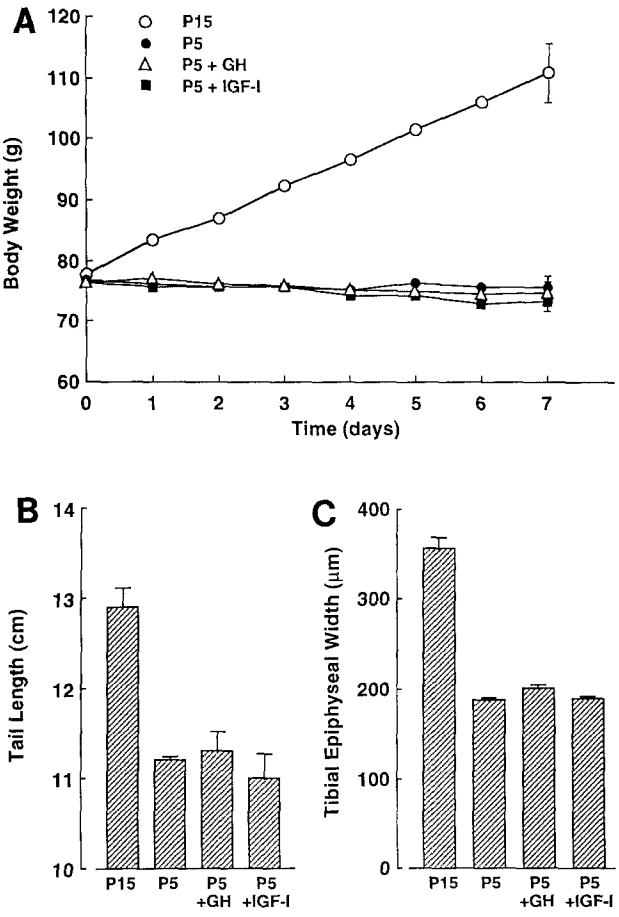

Fig 7. (A) Body weight, (B) tail length, and (C) tibial epiphyseal width in normal protein-fed rats (P15), protein-restricted rats (P5), protein-restricted rats infused with rat GH (200 μg/100 g/d, P5 + GH), and protein-restricted rats infused with recombinant human IGF-I (300 μg/d, P5 + IGF-I). The treatments were 1 week in duration. Values are shown as the mean ± SEM. For these indices of growth, P15 animals were significantly greater than P5 animals (P < .01). Reprinted with permission.[71] The Endocrine Society.

participate in the growth arrest that accompanies protein restriction; (2) IGF-I mediates the stimulatory effects of GH on IGFBP-3 synthesis; and (3) exogenous GH does not restore normal responsiveness to exogenous IGF-I in protein-restricted rats.

CONCLUSIONS

IGF-I is GH-dependent, but nutritional factors also play an important role in its regulation. In this review, we have presented various aspects of nutritional regulation of IGF-I in humans. We suggest that IGF-I measurements in serum have a role in the assessment of nutritional status of patients. In animal studies, the low IGF-I levels occurring during dietary restriction are associated with GH resistance. We have investigated the mechanisms underlying this resistance in fasted and protein-deprived rats. Our studies show that nutrient availability regulates GH action at multiple levels: liver GH receptor regulation, GH postreceptor events, and IGF-I gene expression. Protein deprivation also accelerates IGF-I clearance, modifies IGF-I interaction with binding proteins, and attenuates expression of biological actions of IGF-I.

REFERENCES

1. Baumann G: Growth hormone heterogeneity: Genes, isohormones, variants and binding proteins. Endocr Rev 12:424-449, 1991

2. Sara VR, Hall K: Insulin-like growth factors and their binding proteins. Physiol Rev 70:591-614, 1990

3. Daughaday WH, Rotwein P: Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. Endocr Rev 10:68-91, 1989

4. Humbel RE: Insulin-like growth factors I and II. Eur J Biochem 190:445-462, 1990

5. Rechler MM, Nissley SP: Insulin-like growth factors, in Sporn MB, Roberts AB (eds): Peptides Growth Factors and Their Receptors, vol 1. Berlin, Germany, Springer-Verlag, 1990, pp 263-367

6. D'Ercole AJ, Stiles AD, Underwood LE: Tissue concentrations of somatomedin-C: Further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. Proc Natl Acad Sci USA 81:935-939, 1984

7. Han VKM, D'Ercole AJ, Lund PK: Cellular location of somatomedin (insulin-like growth factor) messenger RNA in the human fetus. Science 236:193-197, 1987

8. McConaghey P, Sledge CB: Production of "sulphation factor" by the perfused liver. Nature 225:1249-1250, 1970

9. Schwander JC, Hauri C, Zapf J, et al: Synthesis and secretion of insulin-like growth factor and its binding protein by the perfused rat liver: Dependence on growth hormone status. Endocrinology 113:297-305, 1983

10. Miller LL, Schalch DS, Draznin B: Role of the liver in regulating somatomedin activity: Effects of streptozotocin diabetes and starvation on the synthesis and release of insulin-like growth factor and its carrier protein by the isolated perfused rat liver. Endocrinology 108:1265-1271, 1981

11. Furlanetto RW, Underwood LE, Van Wyk JJ, et al: Estimation of somatomedin-C levels in normals and patients with pituitary disease by radioimmunoassay. J Clin Invest 60:648-657, 1977

12. Rechler MM, Nissley SP: The nature and regulation of the receptors for insulin-like growth factors. Annu Rev Physiol 47:425-442, 1985

13. Van Wyk JJ: The somatomedins: Biologic actions and physiologic control mechanisms, in Li CH (ed): Hormonal Proteins and Peptides. New York, NY, Academic, 1984, pp 81-125

14. Underwood LE, D'Ercole AJ, Clemmons DR, et al: Paracrine functions of somatomedins. Clin Endocrinol Metab 15:59-77, 1986

15. Holly JMP, Wass JAH: Insulin-like growth factors: Autocrine, paracrine or endocrine? New perspectives of the somatomedin hypothesis in the light of recent developments. J Endocrinol 122:611-618, 1989

16. Salmon WD, Daughaday WH: A hormonally-controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. J Lab Clin Med 49:825-836, 1957

17. Shimasaki S, Ling N: Identification and molecular characterization of insulin-like growth factor binding proteins (IGFBP-1,-2,-3,-4,-5 and -6). Prog Growth Factor Res 3:243-266, 1992

18. Martin JL, Baxter RC: Insulin-like growth factor binding protein-3: Biochemistry and physiology. Growth Regul 2:88-99, 1992

19. Baxter RC, Martin JL, Beniac VA: High molecular weight insulin-like growth factor binding protein complex: Purification and properties of the acid-labile subunit from human serum. J Biol Chem 264:11843-11848, 1989

20. Baxter RC, Martin JL: Structure of the M_r 140,000 growth hormone–dependent insulin-like growth factor binding protein complex: Determination by reconstitution and affinity-labelling. Proc Natl Acad Sci USA 86:6898-6902, 1989

21. Clemmons DR: Insulin-like growth factors binding proteins, in LeRoith D (ed): Insulin-Like Growth Factors: Molecular and Cellular Aspects. Boca Raton, FL, CRC, 1991, pp 151-179

22. Copeland KC, Underwood LE, Van Wyk JJ: Induction of immunoreactive somatomedin-C in human serum by growth hormone: Dose response relationships and effect on chromatographic profiles. J Clin Endocrinol Metab 50:690-697, 1980

23. Winter RJ, Phillips LS, Green OC, et al: Somatomedin activity in the Mauriac syndrome. J Pediatr 97:598-600, 1980

24. Maes M, Ketelslegers JM, Underwood LE: Low plasma somatomedin-C in streptozocin-induced diabetes mellitus: Correlation with changes in somatogenic and lactogenic liver binding sites. Diabetes 32:1060-1064, 1983

25. Maes M, Underwood LE, Ketelslegers JM: Low serum somatomedin-C in insulin-dependent diabetes: Evidence for a post-receptor mechanism. Endocrinology 118:377-382, 1986

26. Grant DB, Hambley J, Becker D, et al: Reduced sulphation factor in undernourished children. Arch Dis Child 48:596-600, 1973

27. Hintz RL, Suskind R, Amatayakul K, et al: Plasma somatomedin and growth hormone values in children with protein calorie malnutrition. J Pediatr 92:153-156, 1978

28. Smith IF, Latham MC, Azabuike JA, et al: Blood plasma levels of cortisol, insulin, growth hormone and somatomedin in children with marasmus, kwashiorkor, and intermediate forms of protein-energy malnutrition. Proc Soc Exp Biol Med 167:607-611, 1981

29. Soliman AT, Hassan AE, Aref MK, et al: 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 20:1122-1130, 1986

30. Rappaport R, Prevot C, Czernichow P: Somatomedin activ-

ity and growth hormone secretion. I. Changes related to body weight in anorexia nervosa. Acta Paediatr Scand 69:37-41, 1980

31. Counts DR, Gwirtsman H, Carlsson LM, et al: The effect of anorexia nervosa and refeeding on growth hormone–binding protein, the insulin-like growth factors (IGFs), and the IGF-binding proteins. J Clin Endocrinol Metab 75:762-767, 1992

32. Kirschner BS, Sutton MM: Somatomedin-C levels in growth-impaired children and adolescents with chronic inflammatory bowel disease. Gastroenterology 91:830-836, 1986

33. Salbe AD, Kotler DP, Wang J, et al: Predictive value of IGF-I concentrations in HIV-infected patients. Clin Res 39:385A, 1991 (abstr)

34. Clemmons DR, Klibanski A, Underwood LE, et al: Reduction of plasma immunoreactive somatomedin-C during fasting in humans. J Clin Endocrinol Metab 53:1247-1250, 1981

35. Isley WL, Underwood LE, Clemmons DR: Dietary components that regulate serum somatomedin-C concentrations in humans. J Clin Invest 71:175-182, 1983

36. Isley WL, Underwood LE, Clemmons DR: Changes in plasma somatomedin-C in response to ingestion of diets with variable protein and energy content. JPEN 8:407-411, 1984

37. Clemmons DR, Seek M, Underwood LE: Supplementary essential amino acids augment the somatomedin-C/insulin-like growth factor I response to refeeding after fasting. Metabolism 34:391-395, 1985

38. Clemmons DR, Underwood LE, Dickerson RN, et al: Use of somatomedin-C/insulin-like growth factor I measurements to monitor nutritional repletion in malnourished patients. Am J Clin Nutr 4:191-198, 1985

39. Unterman TG, Vazquez RM, Sla AJ, et al: Nutrition and somatomedia. XII. Usefulness of somatomedin-C in nutritional assessment. Am J Med 78:228-234, 1985

40. Colletti RB, Copeland KC, Devlin JT, et al: Effect of obesity on plasma insulin-like growth factor-I in cancer patients. Int J Obes 15:523-527, 1991

41. Wilson DM, Killen JD, Hammer LD, et al: Insulin-like growth factor-I as a reflection of body composition, nutrition and puberty in sixth and seventh grade girls. J Clin Endocrinol Metab 73:907-912, 1991

42. Sullivan DH, Carter WJ: Insulin-like growth factor I as an indicator of protein-energy undernutrition among metabolically stable hospitalized elderly. J Am Coll Nutr 13:184-191, 1994

43. Forbes GB, Brown MR, Welle SL, et al: Hormonal response to overfeeding. Am J Clin Nutr 49:608-611, 1989

44. Marin P, Kvist H, Lindstedt G, et al: Low concentrations of insulin-like growth factor-I in abdominal obesity. Int J Obes 17:83-89, 1993

45. Rasmussen MH, Frystyk J, Andersen T, et al: The impact of obesity, fat distribution, and energy restriction on insulin-like growth factor-I (IGF-I), IGF-binding protein-3, insulin, and growth hormone. Metabolism 43:315-319, 1994

46. Ho KY, Veldhuis JD, Johnson ML, et al: Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man. J Clin Invest 81:968-975, 1988

47. Merimée TJ, Zapf J, Froesch ER: Insulin-like growth factors in the fed and fasted states. J Clin Endocrinol Metab 55:999-1002, 1982

48. Phillips LS, Young HS: Nutrition and somatomedin. I. Effect of fasting and refeeding on serum somatomedin activity and cartilage growth activity in rats. Endocrinology 99:304-314, 1976

49. 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 97:243-252, 1983

50. Maes M, Underwood LE, Ketelslegers JM: Low serum somatomedin-C in protein deficiency: Relationship with changes in liver somatogenic and lactogenic binding sites. Mol Cell Endocrinol 37:301-309, 1984

51. Baxter RC, Bryson JM, Turtle JR: The effect of fasting on liver receptors for prolactin and growth hormone. Metabolism 30:1086-1090, 1981

52. Postel-Vinay MC, Cohen-Tough E, Charrier J: Growth hormone receptors in rat liver membranes: Effect of fasting and refeeding and correlation with plasma somatomedin activity. Mol Cell Endocrinol 28:657-669, 1982

53. Straus DS, Takemoto CD: Effect of fasting on insulin-like growth factor-I (IGF-I) and growth hormone receptor mRNA levels and IGF-I gene transcription in rat liver. Mol Endocrinol 4:91-100, 1990

54. Maiter D, Maes M, Underwood LE, et al: Early changes in serum concentrations of somatomedin-C induced by dietary protein deprivation in rats: Contributions of growth hormone receptor and post-receptor defects. J Endocrinol 118:113-120, 1988

55. Fliesen T, Maiter D, Gerard G, et al: Reduction of serum insulin-like growth factor-I by dietary protein restriction is age dependent. Pediatr Res 26:415-419, 1989

56. Thissen JP, Triest S, Underwood LE, et al: Divergent responses of serum insulin-like growth factor-I and liver growth hormone (GH) receptors to exogenous GH in protein-restricted rats. Endocrinology 126:908-913, 1990

57. Maes M, Amand Y, Underwood LE, et al: 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) 117:320-326, 1988

58. Thissen JP, Triest S, Maes M, et al: The decreased plasma concentration of insulin-like growth factor-I in protein-restricted rats in not due to decreased numbers of growth hormone receptors on isolated hepatocytes. J Endocrinol 124:159-165, 1990

59. Maiter D, Fliesen T, Underwood LE, et al: Dietary protein restriction decreases insulin-like growth factor I independent of insulin and liver growth hormone binding. Endocrinology 124:2604-2611, 1989

60. Thissen JP, Pucilowska JB, Underwood LE: Differential regulation of insulin-like growth factor I (IGF-I) and IGF binding protein-1 messenger ribonucleic acids by amino acid availability and growth hormone in rat hepatocyte primary culture. Endocrinology 134:1570-1576, 1994

61. Phillips LS, Goldstein S, Pao CI: Nutrition and somatomedin. XXVI. Molecular regulation of IGF-I by insulin in cultured rat hepatocytes. Diabetes 40:1525-1530, 1991

62. Harp JB, Goldstein S, Phillips LS: Molecular regulation of IGF-I by amino acid availability in cultured hepatocytes. Diabetes 40:95-101, 1991

63. Thissen JP, Triest S, Moats-Staats BM, et al: Evidence that pretranslational and translational defects decrease serum insulin-like growth factor-I concentrations during dietary protein restriction. Endocrinology 129:429-435, 1991

64. Emler CA, Schalch DS: Nutritionally-induced changes in hepatic insulin-like growth factor-I (IGF-I) gene expression in rats. Endocrinology 120:832-838, 1987

65. Moats-Staats BM, Brady JL, Underwood LE, et al: Dietary protein restriction in artificially-reared neonatal rats causes a reduction of insulin-like growth factor I (IGF-I) gene expression. Endocrinology 125:2368-2374, 1989

66. Bornfeldt KE, Arnqvist HJ, Enberg B, et al: Regulation of

insulin-like growth factor-I and growth hormone receptor gene expression by diabetes and nutritional state in rat tissues. J Endocrinol 122:651-656, 1989

67. VandeHaar M, Moats-Staats BM, Davenport ML, 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 103:305-312, 1991

68. Lowe WL Jr, Adamo M, Werner H, et al: Regulation by fasting of rat insulin-like growth factor I and its receptor. Effects on gene expression and binding. J Clin Invest 84:619-626, 1989

69. Thissen JP, Underwood LE: Translational status of the insulin-like growth factor-I mRNA in liver of protein-restricted rats. J Endocrinol 132:141-147, 1992

70. Thissen JP, Davenport ML, Pucilowska JB, et al: Increased serum clearance and degradation of ^{125}I-labeled IGF-I in protein-restricted rats. Am J Physiol 262:E406-E411, 1992

71. Thissen JP, Underwood LE, Maiter D, et al: Failure of insulin-like growth factor-I (IGF-I) infusion to promote growth in protein-restricted rats despite normalization of serum IGF-I concentrations. Endocrinology 128:885-890, 1991

72. Thissen JP, Underwood LE, Vanderijst JF, et al: Anabolic effects of combined exogenous GH/IGF-I in protein restricted rats. Growth Regul, p 89, 1994 (abstr 1162)

73. Philipps AF, Persson B, Hall K, et al: The effects of biosynthetic insulin-like growth factor-I supplementation on somatic growth, maturation, and erythropoiesis in the neonatal rat. Pediatr Res 23:298-305, 1988

74. O'Sullivan U, Gluckmann PD, Breier BH, et al: Insulin-like growth factor-I (IGF-I) in mice reduces weight loss during starvation. Endocrinology 125:2793-2794, 1989

75. Asakawa K, Hizuka N, Takano K, et al: Effects of insulin-like growth factor-I or human growth hormone in fasted rats. Growth Regul 2:40-44, 1992