Effect of Intravenous Insulin-like Growth Factor I in Two Patients with Leprechaunism

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ABSTRACT

Leprechaunism (Donohue syndrome) is an autosomal recessive disorder characterized by hyperglycemia, extreme insulin resistance, dysmorphic features, failure to thrive, and early death. In this study, recombinant IGF-I, which has both insulin-like and anabolic effects, was administered to two infants with leprechaunism in an attempt to reduce hyperglycemia and improve nutritional status. IGF-I was infused for 66 h in patient FL-1 and 62 h in patient NC-2, with maximal infusion rates of 110 and 40 $\mu\text{g/kg/h}$, respectively. Although supraphysiologic concentrations of IGF-I were achieved (459 and 1583 $\mu\text{g/L}$ in FL-1 and NC-2, respectively), there were no apparent glucose-lowering or nitrogen-sparing effects. Insulin concentrations decreased from extremely high values (16804 and 10224 pmol/L) but remained elevated (611 pmol/L in FL-1 and

5869 pmol/L in NC-2). No changes in serum and urinary urea nitrogen or electrolytes occurred. IGF binding protein-2, which was the predominant IGF binding protein in serum by ligand blot and immunoblot, did not change with IGF-I infusion. IGF binding protein-3 levels were low at baseline and increased slightly during the infusion. We hypothesize that the lack of significant glucose-lowering and anabolic responses to IGF-I could be secondary to a postreceptor defect in IGF-I signaling resulting from the absence of functional insulin receptors. (*Pediatr Res* 36: 749-754, 1994)

Abbreviations

GH, growth hormone

IGFBP, insulin-like growth factor binding protein

Leprechaunism (Donohue syndrome), a genetic disorder characterized by extreme insulin resistance, intrauterine growth retardation, dysmorphic features, and lipodystrophy (1-3), is associated with defects in insulin binding, insulin receptor autophosphorylation, and kinase activity (4). Various point mutations in the insulin receptor gene have been identified in affected patients (5, 6), and some patients also have functional abnormalities of receptors for IGF-I and epidermal growth factor (7-9). Variations in defects of the insulin receptor and receptor signaling mechanisms may explain the phenotypic heterogeneity of the leprechaunism syndrome, with some pa-

tients surviving for several years and others dying in early infancy.

IGF-I is structurally similar to insulin, and IGF-I receptors are homologous with insulin receptors, with which they form hybrid receptors. IGF-I has glucose-lowering as well as anabolic actions: it mediates most of the growth-promoting actions of GH, causes weight gain in hypophysectomized rats (10, 11), and is anabolic in humans with GH insensitivity syndrome (12) and calorie-restricted normal volunteers (13). We therefore examined the short-term metabolic effects of IGF-I administered i.v. in two patients with leprechaunism to determine whether this peptide might serve as a substitute for insulin in these patients by reducing blood glucose and producing an anabolic response.

METHODS

Patient FL-1 is a white female who was the product of a nonconsanguineous marriage and a 37-wk unremarkable pregnancy, labor, and delivery. Her birth weight was 1.8 kg, length 44.5 cm, and head circumference 30 cm (all < 5th percentile). At 3 wk of age, she was observed to

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have hyperglycemia (23.4 mmol/L or 422 mg/dL); decreased fat stores; a small, triangular face; a depressed nasal bridge; a small mandible; thick lips; and gingival hyperplasia. She had breast tissue hyperplasia, a distended abdomen without organomegaly, a prominent clitoris and prominent labia majora, and generalized hirsutism. An echocardiogram, obtained to investigate a heart murmur, showed left ventricular hypertrophy and a small atrial septal defect. Ultrasonography of the pelvic area demonstrated bilateral ovarian cysts. A randomly obtained blood sample revealed an extremely elevated insulin concentration of 2870 pmol/L (normal 35–145 pmol/L) and a C-peptide of 20 μ g/L (normal 0.8–4.0 μ g/L). IGF-I serum concentration was 7.5 μ g/L (normal 17–248 μ g/L) and glycosylated Hb 7.3% (normal 4.6–7.3%).

During the second month of life, neither several days of s.c. administration of exogenous regular insulin (maximum 10 U/kg/d), nor i.v. infusion of insulin (maximum rate of 1.4 U/kg/h) lowered blood glucose. On a low-carbohydrate diet, her glucose concentrations were 5.6–16.7 mmol/L (100–300 mg/dL). During her first 6 months of life she had worsening hirsutism, rectal prolapse, gastroesophageal reflux and slow growth with delayed mental and motor development. She received the trial of recombinant IGF-I at 8 mo of age.

Patient NC-2 is of Afghani descent and was the product of first cousins and a 38-wk pregnancy complicated by insulin-dependent gestational diabetes. His birth weight was 1.53 kg, length 42 cm, and head circumference 32 cm (all < 5th percentile). He had a small face with prominent eyes, wide nostrils, large ears, thick lips with prominent rugae, a small chin, and increased facial hair. He had prominent breast tissue and a distended abdomen with poorly developed abdominal wall musculature. As part of an evaluation for a cardiac murmur, an ECG showed left ventricular hypertrophy, and an echocardiogram demonstrated subaortic stenosis and mild mitral regurgitation. He had cholestatic jaundice with fat malabsorption, hepatomegaly, and rectal prolapse. His phallus was enlarged (4.4 cm stretched; mean $\pm$ SD for term male is 3.5 $\pm$ 0.4 cm). He had hyperpigmented, loose, wrinkled skin; generalized hypertrichosis; acanthosis nigricans in the cervical, axillary, and inguinal regions; and dysplastic nails. While receiving continuous nasogastric tube feedings to avoid fasting hypoglycemia, his glucose concentration ranged between 11 and 16 mmol/L (200–300 mg/dL). Measured insulin concentrations were 8 093, 12 650, and 15 943 pmol/L (normal 35–145 pmol/L). IGF-I concentrations were extremely low, ranging between 2 and 3 μ g/L. Exogenous regular insulin, at a maximum dose of 1 U/kg i.v. given 5 d before the IGF-I trial, did not influence serum glucose values (14.0 mmol/L at baseline and 13.0, 13.3, 13.6, and 12.8 mmol/L at 15, 30, 45, and 60 min, respectively).

When given IGF-I at 5 mo of age, his length (52.5 cm) and weight (3.57 kg) were below the 5th percentile, although height velocity and head growth were close to

normal. Molecular analyses of skin fibroblasts indicated that he is homozygous for a deletion of both alleles of the insulin receptor gene (14).

The experimental protocols were approved by the Committees for the Protection of the Rights of Human Subjects at the University of Miami and the University of North Carolina at Chapel Hill, and written, informed consent was obtained from the parents.

Patient FL-1 was given a 5% dextrose solution i.v. at 25% of the maintenance rate. Her oral intake of formula was 180–190 kcal/kg/d. Blood for baseline studies was obtained, and capillary glucose concentrations were determined every 3 h (Chemstrip BG, Accu-Check II, Boehringer-Mannheim, Indianapolis, IN). After 4 d, a continuous i.v. infusion of recombinant human IGF-I (gift from Genentech Inc., South San Francisco, CA) diluted in physiologic saline was begun at a dose of 4 μ g/kg/h and increased every 4 h by 10 μ g/kg/h (if glucose levels did not fall below 5.6 mmol/L) to a maximal infusion rate of 110 μ g/kg/h. Blood glucose concentrations were monitored every 1–2 h during the infusion. Serum electrolytes, urea nitrogen, creatinine, insulin, IGF-I, IGF-II, IGFBP, and GH were measured daily. Twenty-four-hour urine collections were obtained for measurement of excretion of urea nitrogen, creatinine, and electrolytes. Glucose, serum and urinary electrolytes, urea nitrogen, and creatinine were measured by standard automated techniques. Serum concentrations of IGF-I and IGF-II were measured by RIA after the binding proteins were removed by C-18 Sep-pak extraction (Waters Associates, Milford, MA) (15, 16). Serum GH (Nichols Institute, San Juan Capistrano, CA) and insulin (Binax Corp., South Portland, ME) were measured by RIA from kits. Ligand blotting was performed for evaluation of IGFBP as previously described (17). Serum was subjected to SDS-PAGE under nonreducing conditions, transferred to nitrocellulose paper, and incubated overnight with a mixture of [¹²⁵I]IGF-I and [¹²⁵I]IGF-II (18). IGFBP were visualized by autoradiography and quantified by scanning densitometry. Some filters were also immunoblotted with antiserum to IGFBP-2 (provided by Dr. David R. Clemmons, University of North Carolina) as previously described (19). Antibody binding was visualized using an alkaline phosphatase-conjugated antibody detection system (Promega Corp., Madison, WI).

Patient NC-2 was fed formula continuously through a nasogastric tube, receiving 230 kcal/kg/d. After 4 d of observation, recombinant human IGF-I (Genentech) diluted in physiologic saline was infused at gradually increasing doses over a 48-h period to a dose of 40 μ g/kg/h. Capillary glucose concentrations were measured using a One Touch II glucometer system (Lifescan Inc., Milpitas, CA). Blood was collected at 0900 and 2100 h daily for measurement of serum glucose, urea nitrogen, creatinine, electrolytes, insulin, IGF-I, IGF-II, IGFBP, and GH. Urine electrolytes, urea nitrogen, and creatinine were also determined. Ligand blot and immunoblot anal-

yses of the IGFBP were performed using plasma samples.

RESULTS

The IGF-I infusion in patient FL-1 ended after 66 h when venous access was lost. At that time, she had received IGF-I at a maximal rate of 110 $\mu\text{g/kg/h}$ for 2 h (Fig. 1, top panel). Caloric intake, urinary output, and body weight (4.8 kg) did not change. The IGF-I infusion in patient NC-2 was stopped after 62 h because he developed congestive heart failure, most likely secondary to fluid and salt overload superimposed on his hypertrophic cardiomyopathy. His weight had increased from 3.57 to 3.90 kg, and he showed pitting edema in the dependent areas. The maximum infusion rate in this child was 40 $\mu\text{g/kg/h}$ (Fig. 2, top panel).

Serum IGF-I concentrations in FL-1 increased from a low baseline value of 7.5 $\mu\text{g/L}$ to a maximum of 459.0 $\mu\text{g/L}$ on the second day of infusion and returned to 9.2 $\mu\text{g/L}$ within 24 h after the IGF-I infusion was stopped

Figure 1. IGF-I infusion rates (bar graph in top panel) and serum concentrations of IGF-I, glucose, insulin, urea nitrogen, and calcium and 24-h urinary excretion of urea nitrogen and calcium in FL-1. The urine values are depicted by bars. The shaded area represents the IGF-I infusion period. Achievement of supraphysiologic serum IGF-I concentrations did not cause a decline in blood glucose values. In contrast, serum insulin concentrations decreased. The IGF-I infusion did not cause a sustained decrease in serum urea nitrogen or urinary urea nitrogen excretion.

Figure 2. IGF-I infusion rates and serum concentrations of IGF-I, glucose, insulin, urea nitrogen, and calcium and 24-h urinary excretion of urea nitrogen and calcium in NC-2. The urine values are depicted by bars. The shaded area represents the IGF-I infusion period. Achievement of supraphysiologic serum IGF-I concentrations did not cause the blood glucose to decline, but insulin levels decreased to 40% of maximum values during the IGF-I infusion and rose to pretreatment levels after its discontinuation. The IGF-I infusion did not cause a change in either serum urea nitrogen or urinary urea nitrogen, nor did it affect the serum calcium concentration or urinary calcium excretion.

(Fig. 1, top panel). Serum IGF-II levels were 240.0 $\mu\text{g/L}$ at baseline (normal $419.0 \pm 145.0 \mu\text{g/L}$), decreased to 84.0 $\mu\text{g/L}$ after 2 d of infusion, and returned to baseline values (300.0 $\mu\text{g/L}$) within 6 h of discontinuation of infusion. Although frequent sampling of GH was not possible, daily GH levels did not change ($<0.6 \mu\text{g/L}$ before, during, and after the IGF-I infusion). In NC-2, serum IGF-I concentrations were 2.3 and 2.9 $\mu\text{g/L}$ at baseline, increased to 1583.0 $\mu\text{g/L}$ at the maximal infusion rate (40 $\mu\text{g/kg/h}$), and decreased to baseline within 12 h after the infusion was stopped (Fig. 2, top panel). Baseline IGF-II values decreased from 97.0 and 166.0 (mean 132.0) $\mu\text{g/L}$ to $44.0 \pm 25.0 \mu\text{g/L}$ during the infusion and returned to baseline range within 12 h after discontinuation of infusion ($129.0 \pm 24.0 \mu\text{g/L}$). GH levels were not affected by the infusion ($<0.7 \mu\text{g/L}$).

Effects on carbohydrate metabolism. Despite achieving supraphysiologic concentrations of IGF-I, blood glucose levels were not significantly altered in either patient.

FL-1 experienced wide fluctuations in glucose values before and during the IGF-I infusion. Hyperglycemia was noted after each feeding. Blood glucose concentrations were more stable in NC-2, who received constant enteral feedings, but all values were above normal [9.7–15.8 mmol/L (174 to 284 mg/dL)]. Insulin concentrations decreased from a pretreatment value of 16 804 pmol/L to 611 pmol/L in FL-1 and from 10 224 to 5 869 pmol/L in NC-2. Within 24 h after discontinuing IGF-I, the insulin concentrations rose to preinfusion values (Figs. 1 and 2, second panel).

Anabolic effects. Infusion of IGF-I did not exert anabolic effects in either patient; no decrease in serum urea nitrogen or urinary urea nitrogen excretion was observed (Figs. 1 and 2, third panel). Although serum calcium did not change, the urinary excretion of calcium increased on the second day of the IGF-I infusion in FL-1 and remained elevated postinfusion. No change in serum or urinary calcium was observed in NC-2 (Figs. 1 and 2, lower panel). No changes were observed in serum and urinary electrolytes or in creatinine clearance in either patient.

IGFBP. By ligand blot analysis, the predominant IGFBP in the serum or plasma of both patients exhibited an M_r of approximately 32 000 (Fig. 3). This band immunostained, with intensity comparable to the ligand blot signal, with a specific antibody raised against human IGFBP-2, making its identity likely IGFBP-2 (data not shown). A lighter band apparent at M_r 45 000 is consistent with IGFBP-3. Densitometric analyses of the ligand blots revealed no consistent changes in the 32 000- M_r

binding protein for either patient, but a 50% increase in IGFBP-3 was observed in NC-2 during the IGF-I infusion (Fig. 3B). Only plasma of NC-2 was available for RIA of the IGFBP. Baseline concentrations of IGFBP-2 by RIA for NC-2 were elevated at 1.08 and 1.47 (mean 1.28) mg/L compared with normal, age-matched controls (0.26 ± 0.08 mg/L) and did not change significantly during IGF-I infusion (1.09 ± 0.31 mg/L). In contrast, baseline IGFBP-3 concentration (0.20 mg/L) was low for chronological age (normal 0.70–2.30 mg/L) and increased to a maximal value of 0.38 mg/L (mean 0.28 ± 0.09 mg/L) during IGF-I infusion.

DISCUSSION

IGF-I promotes growth and differentiation of cells and mediates the anabolic effects of GH in animals (10) and humans (12). In hypophysectomized rats, IGF-I increases muscle protein content (10) and stimulates growth of cartilage and bone (20). IGF-I also decreases blood glucose, acting with approximately 6% the potency of insulin (21). In our two patients with leprechaunism, however, serum glucose remained elevated and no significant nitrogen-sparing effect was apparent after achieving supraphysiologic serum concentrations of IGF-I. We hypothesize that the ability of patients with insulin resistance to respond to IGF-I is determined by the degree and manner in which their underlying molecular defect in the insulin receptor gene interferes with normal insulin action. NC-2, who has a homozygous deletion of the insulin receptor gene, is predicted to have no insulin receptors (14). The specific molecular defect in FL-1 has not been determined, although mutations of the insulin receptor gene in other patients have been shown to impair receptor biosynthesis or transport to the cell surface, decrease the affinity of insulin binding, impair tyrosine kinase activity, or accelerate receptor degradation (22).

The inability of IGF-I to produce significant anabolic or glycemic effects in our patients differs from the findings of several recent reports in which IGF-I administration produced metabolic effects in patients with other syndromes of insulin resistance (23–25) and in patients with diabetes mellitus (26, 27). Kuzuya *et al.* (28) reported that s.c. injections of IGF-I (100–400 μ g/kg twice daily) for up to 16 mo in patients with type A insulin resistance syndrome or congenital generalized lipodystrophy result in reduced glucose and insulin levels and sustained decreases in fructosamine and glycosylated Hb. However, two of their patients with leprechaunism (0.6 and 7 y old) did not have improved glycemic control during IGF-I treatment despite decreased serum insulin concentrations and an apparent initial response to acute s.c. administration of IGF-I (100–300 μ g/kg).

The failure of FL-1 and NC-2 to respond appropriately to IGF-I is enigmatic. Virilization and acanthosis nigricans, observed in most patients with this disease as well as our patients, may result from excessive concentrations of insulin acting through IGF-I receptors rather than from

Figure 3. Effect of IGF-I infusions on IGFBP in two patients with leprechaunism. *A*, Ligand blot of plasma collected from FL-1. From left to right: the first day is preinfusion (baseline), d 2 to 4 are during IGF-I, and d 5 and 6 are post-IGF-I infusion. IGFBP-2 levels are high for age, and no significant change was observed during the infusion. A modest increase in IGFBP-3 could be quantified when the ligand blot was exposed for a longer period of time (not shown). IGFBP from three age-matched controls are shown on the right. There is significant variability in the IGFBP profile, with IGFBP-2 levels being much lower than in our patients. *B*, Ligand blot of plasma collected from NC-2. From left to right: d 1 and 2 are pretreatment (baseline), d 3 to 5 are during IGF-I infusion, and the last two lanes (d 6 and 7) are postinfusion samples. No significant changes in the already high IGFBP-2 levels were noted, but a 50% increase in IGFBP-3 was measured with densitometry (d 4 and 5).

residual insulin receptor function (29, 30). The complete absence of insulin receptors in NC-2 supports this hypothesis. Although it is possible that insulin in our patients is acting through unknown mechanisms or interacts with an unidentified receptor (31), some IGF-I receptor signaling appears likely in these patients.

Several mechanisms should be considered to explain the failure of short-term infusions of IGF-I to exert effects in our patients. Their insulin receptor defects alone do not likely explain their failure to respond (Fig. 4, site 1), because they should have intact IGF-I receptors through which IGF-I would exert its effect. In NC-2, who is presumed to have no insulin receptors, we might anticipate impaired glycemic responses to IGF-I if some of the insulin-like effects of IGF-I are normally exerted through the insulin receptor. We would not, however, expect impaired anabolic responses, which should be mediated through the IGF-I receptor.

Attenuated or absent responses to IGF-I administration in our patients could therefore be secondary to defects in IGF-I binding (Fig. 4, site 3) or postreceptor signaling (Fig. 4, site 4). We assume that the IGF-I receptor is structurally normal because it is unlikely that our patients have two separate genetic defects. However, subnormal (7) as well as normal (32, 33) binding of IGF-I to the IGF-I receptor has been reported in patients with leprechaunism. Most likely, a defect in IGF-I postreceptor signaling (Fig. 4, site 4) explains the minimal responses in our patients. Myers *et al.* (34) showed that insulin and IGF-I share a common initial signaling pathway, at least to the level of interaction between insulin receptor substrate-1 and phosphatidylinositol 3-kinase. Signaling pathways distal to insulin receptor substrate-1

diverge and probably explain the apparent differences in insulin and IGF-I receptor actions, but each may rely on one another for normal function.

Differences in the ability to form functional insulin/IGF hybrid receptors might also contribute to the heterogeneity in the response of insulin-resistant patients to insulin or IGF-I (Fig. 4, site 2). Although the signaling properties and biochemical effects of these hybrid receptors are not fully understood (35–37), failure of their formation in NC-2 would prohibit an IGF-I effect through this pathway.

Alternative explanations for the failure of our patients to respond appropriately to IGF-I infusion include competitive inhibition of IGF-I binding by extraordinarily high insulin concentrations (Fig. 4, site 5) and high circulating levels of unsaturated IGFBP-2 decreasing access of IGF-I to its receptor (Fig. 4, site 6). It seems unlikely that these mechanisms would prevent IGF-I actions completely when such high IGF-I serum values were achieved. The hypoglycemic response to infused IGF-I occurs within 1–2 h, often at lower doses than used here. It therefore seems unlikely that the duration of IGF-I infusion was too brief. However, calciuria increased in FL-1 during the IGF-I infusion, so we cannot exclude the possibility that more prolonged treatment would result in an anabolic effect.

Despite the absence of a glycemic or significant anabolic response to IGF-I, some changes were observed. Insulin and IGF-II concentrations decreased, whereas IGFBP-3 levels increased modestly in NC-2. Some of these effects may have been mediated via the IGF-I receptor. Because IGF-I and IGF-II are largely bound to the same IGFBP, it is probable that the decrease in IGF-II during the IGF-I infusion is the result of its displacement from IGFBP-2 and increased clearance from plasma. The increase in IGFBP-3 may be due to increased stability of this binding protein in the presence of increased IGF-I (38). The decrease in serum insulin appears to be relatively independent of changes in plasma glucose, and is thought to be mediated by a direct effect of IGF-I on pancreatic β -cells. Decreased insulin production occurs in rats in which euglycemia is maintained during IGF-I infusion (39, 40) and has also been shown in humans (12, 25). It is believed that this effect is mediated by the IGF-I receptor.

In summary, short-term i.v. infusions of IGF-I in two patients with extreme insulin resistance did not improve hyperglycemia or anabolism despite decreasing insulin concentrations. Our findings suggest that extreme insulin resistance due to defects in the insulin receptor may produce a postreceptor defect in IGF-I action.

Figure 4. Possible mechanisms for absent insulin and IGF-I effects. *IR*, insulin receptor; *IGFR*, type I IGF receptor; *IR/IGFR*, insulin/IGF hybrid receptor; *IRS-1*, insulin receptor substrate-1; *Ptd Ins 3-kinase*, phosphatidylinositol 3-kinase; 1, intrinsic insulin receptor defect; 2, failure to form functional hybrid receptors; 3, defective IGF-I binding to its receptor; 4, postreceptor signaling defect; 5, competitive inhibition of IGF-I binding by insulin; 6, sequestration of IGF-I by IGFBP-2.

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