Growth Hormone Induces Resistance to the Mitogenic Action of Insulin Through Local IGF-I

Studies in Normal and Pygmy T-Cell Lines

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Growth hormone (GH) and insulin have both mitogenic and metabolic actions. The growth-promoting effects of GH in vivo are thought to be mediated by insulin-like growth factor-I (IGF-I), whereas the metabolic effects of GH are thought to be either direct or mediated by factors other than IGF-I. In previous studies using HTLV-II-transformed T-lymphoblast cell lines established from normal individuals, we have shown that GH preincubation induces resistance to the growth-promoting (mitogenic) action of insulin. In this study, using T-cell lines from 3 American control subjects, 1 African control subject, and 1 African Pygmy (the latter previously shown to be resistant to the growth-promoting actions of both IGF-I and GH), we examined the role of local IGF-I in the mediation of GH-induced resistance to the mitogenic action of insulin. In these studies, we quantified the stimulation of T-cell colony formation in response to insulin in the presence and absence of either GH or IGF-I. We found that *1*) GH or IGF-I preincubation of normal T-cell lines completely blunts mitogenic responsiveness to subsequent stimulation with insulin (all $P < 0.001$ versus either no GH or no IGF-I); *2*) pretreatment with a monoclonal antibody against the IGF-I receptor blocks both GH- and IGF-I-induced resistance to the mitogenic action of insulin in normal T-cell lines (both $P =$ NS versus insulin alone); and *3*) neither GH nor IGF-I preincubation induces resistance to the growth-promoting action of insulin in the Pygmy T-cell line ($P = 0.37$ and $P = 0.74$, respectively, versus insulin alone). We conclude from these data that *1*) GH-induced resistance to the mitogenic action of insulin is mediated by local IGF-I, and *2*) the Pygmy T-cell line does not develop insulin resistance in response to GH or IGF-I treatment because of a primary variation in IGF-I receptor function. *Diabetes* 43:68–72, 1994

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GH, growth hormone; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; IGFBP-3, insulin-like growth factor binding protein-3; BMI, body mass index; IL-2, interleukin-2; GHBP, GH-binding protein; RSB, relative specific binding; BSA, bovine serum albumin; PBS, phosphate-buffered saline; IgG_1, immunoglobulin G_1; ANOVA, analysis of variance; αIR-3, IGF-I receptor antibody.

Growth hormone (GH) exerts both mitogenic and metabolic effects. The growth-promoting actions of GH in vivo are thought to be mediated by insulin-like growth factor-I (IGF-I), produced in the liver, cartilage, and almost all tissues examined (1). The metabolic effects of GH are predominantly antagonistic to the metabolic actions of insulin, which leads to decreased glucose utilization and increased lipolysis (2). The ability of GH to induce resistance to the metabolic actions of insulin is not thought to be mediated by IGF-I (2–4). Insulin itself has growth-promoting and metabolic properties in vivo and in vitro (5). By quantifying in vitro colony formation of HTLV-II-transformed T-lymphoblast cell lines established from normal individuals, we have shown previously that GH preincubation induces resistance to the growth-promoting (mitogenic) action of insulin (6). This study, using T-cell lines from normal control subjects and from an African Pygmy, previously shown to be resistant to the growth-promoting actions of both GH and IGF-I (7), was undertaken to elucidate the role of IGF-I in mediating GH-induced resistance to the mitogenic action of insulin, and to determine if the Pygmy T-cell line was resistant to the ability of GH and/or IGF-I to induce resistance to the mitogenic action of insulin.

RESEARCH DESIGN AND METHODS

T-cell lines were established from 2 different Africans, 1 adult male Efe Pygmy and 1 adult male Lese control subject with no known Efe admixture for at least 3

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generations, and from 3 normal adult individuals living in the United States (6). The average adult height of Efe Pygmies is 143 cm (8). Procurement of blood from the normal subjects was performed after obtaining informed consent and with approval of the UCLA Human Subject Protection Committee. Blood from the African subjects was drawn after explaining the nature of the study; because they were illiterate, only verbal consent could be obtained. At the time of study, the Pygmy was estimated to be 27 years of age, was 143.6 cm tall, weighed 46.5 kg, had a body mass index (BMI) of 22.6 kg/m^2, and had a triceps skin-fold thickness of 6.5 mm. The results of plasma studies performed on the Pygmy were as follows: IGF-I = 206 μg/L (*n* = 135–449 μg/L), insulin-like growth factor-II (IGF-II)= 116 μg/L (*n* = 288–736 μg/L), IGF binding protein-3 (IGFBP-3) = 1.9 mg/L (*n* = 1.9–4.2 mg/L), and GH-binding protein (GHBP) = 38% relative specific binding (RSB) (*n* = 54–159% RSB). The African control subject was estimated to be 31 years of age, was 162.4 cm tall, weighed 58.5 kg, had a BMI of 22.2 kg/m^2, and had a triceps skin-fold thickness of 8.0 mm. The results of plasma studies performed on the African control subject were as follows: IGF-I = 126 μg/L, IGF-II = 146 μg/L, IGFBP-3 = 2.1 mg/L, and GHBP = 40% RSB.

T-lymphoblast transformation. Methodology for HTLV-II transformation of peripheral blood lymphocytes has been described previously (9–11). Low-density mononuclear cells (1×10^5/ml) were isolated by Ficoll-Hypaque density-gradient separation of 10 ml of blood, primed overnight with phytohemagglutinin and interleukin-2 (IL-2), and cocultivated with an equal number of lethally irradiated (12,000 cGy) late-passage Mo cells (HTLV-II) (12) in Iscove's medium supplemented with 20% fetal bovine serum and IL-2. A virus-producing, immortalized T-cell line developed in ~4 weeks. Cell lines were fed 2 days before clonogenic studies to ensure that all experiments were conducted with cells in an exponential growth phase. A total of 50,000 transformed T-cells/ml (5×10^3/well) were cultured in methylcellulose in microtiter plates with 1.5% bovine plasma albumin, without addition of IL-2.

Studies of insulin responsiveness after GH or IGF-I preincubation. T-cells in serum-free medium (5×10^5 T-cells/ml) containing 0.1% bovine serum albumin (BSA) (Intergen Biochemicals, Purchase, NY), antibiotics, and dextrose (0.35%) were preincubated for 2 h with either recombinant human GH (50 or 100 μg/L) (Genentech, San Francisco, CA) or recombinant human IGF-I (8 μg/L) (Upstate Biotechnology, Lake Placid, NY). These preincubation conditions were chosen based on results from a series of dose ranges tested for their ability to reproducibly induce subsequent insulin resistance. The cells were then washed twice with a serum-free, albumin-containing medium without GH or IGF-I before plating in methylcellulose containing 1.5% bovine plasma albumin at a final concentration of 5×10^4/ml. Then, either recombinant human insulin (Eli Lilly, Indianapolis, IN) at concentrations of 1.2×10^3, 1.4×10^3, 1.6×10^3, 1.7×10^3, 8.6×10^3, 17.3×10^3, and 43.2×10^3 pM, or phosphate-buffered saline (PBS) at pH 7.40, was added directly to each well on top of the methylcellulose-cell mixture. After 7–10 days, colonies containing a minimum of 8 cells were enumerated using an inverted microscope. Experiments were performed in triplicate, with a replicate variability of <5%.

IGF-I receptor antibody studies. T-cell line clonal responses to insulin after either GH or IGF-I preincubation were quantified in the presence or absence of IGF-I receptor antibody (αIR-3), a monoclonal immunoglobulin G_1 (IgG_1) antibody against the IGF-I receptor (Oncogene Science, Manhasset NY), which was added 1 h before GH or IGF-I preincubation at a final concentration of 5×10^{-4} g/L.

Data analysis. The unstimulated number of T-lymphoblast colonies formed in incubation mixtures without added insulin was defined as 100%. Mean basal colony counts in paired experiments (± GH, ± IGF-I, + GH ± αIR-3, and ± IGF-I + αIR-3) ranged between 31.5 ± 3.2 and 54.8 ± 2.8, differences not previously shown to alter peak responsiveness of normal T-cell lines to insulin, IGF-I, or GH (11,13). Data are presented as the mean ± SE. Statistical comparisons were made by repeated measures two-factor analysis of variance (ANOVA).

RESULTS

Insulin responsiveness after GH preincubation. Verifying our previous findings in American control T-cell lines (11,13), clonal responsiveness of the current American normal (Fig. 1*A*), African normal (Fig. 1*B*), and Pygmy (Fig. 1*C*) T-cell lines to insulin showed two peaks; in all cases the first peak occurred at an insulin concentration of 1.6×10^3 pM and the second peak at an insulin concentration of 17.3×10^3 pM. No significant difference was observed in overall clonal responsiveness to insulin between American and African control T-cell lines ($P = 0.88$ by ANOVA) or between American control and Pygmy T-cell lines ($P = 0.91$). For American control T-cell lines, the mean first-peak response to insulin was 77 ± 3.2% above baseline, and the mean second peak was 79 ± 7.0% above baseline (Fig. 1*A*). For the African control T-cell line, the mean first peak was 79 ± 14.6% above baseline, and the mean second peak was 82 ± 15.0% above baseline (Fig. 1*B*). For the Pygmy T-cell line, the mean first peak was 76 ± 12.5% above baseline, and the mean second peak was 81 ± 18.6% above baseline (Fig. 1*C*). Preincubation of control T-cell lines with GH completely abrogated clonal responsiveness to all insulin concentrations studied (American $P = 0.009$ [Fig. 1*A*] and African $P < 0.0001$ [Fig. 1*B*], respectively, versus no GH). After preincubation of the Pygmy T-cell line with GH, no significant change was found in overall responsiveness to insulin ($P = 0.37$ versus no GH); the mean first peak response was 69 ± 27.6% above baseline, and mean second peak was 63 ± 15.9% above baseline (Fig. 1*C*).

Insulin responsiveness after IGF-I preincubation. As with the GH experiments above, there was no significant difference in overall clonal responsiveness to insulin between American and African control T-cell lines ($P = 0.80$) or between American control and Pygmy

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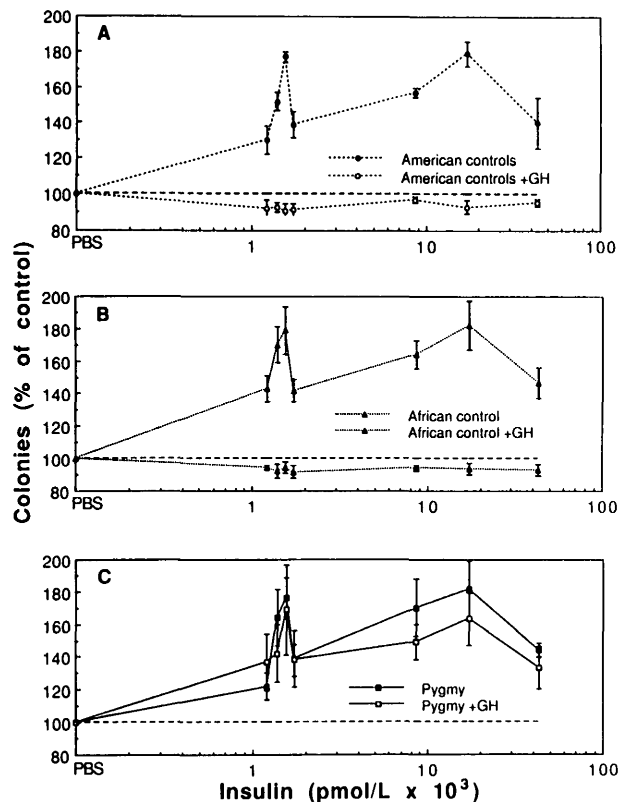

FIG. 1. Insulin responsiveness after GH preincubation. 5 × 10^5 T-cells/ml in serum-free medium containing 0.1% BSA were preincubated for 2 h with recombinant human GH (50 or 100 μg/l). The cells were then washed twice with serum-free, albumin-containing medium without GH before plating in methylcellulose containing 1.5% bovine plasma albumin at a final concentration of 5 × 10^4/ml. Then, either recombinant human insulin at concentrations from 1.2 × 10^3 to 43.2 × 10^3 pM, or PBS at pH 7.40, was added directly to each well on top of the methylcellulose-cell mixture. After 7–10 days, colonies containing a minimum of 8 cells were enumerated using an inverted microscope. *A*: Clonal responsiveness to insulin of American control T-cell lines was completely abrogated after preincubation with GH. *B*: Clonal responsiveness to insulin of the African control T-cell line was also completely blocked after preincubation with GH. *C*: Clonal responsiveness to insulin of the Pygmy T-cell line, however, was not significantly reduced after preincubation with GH. In all figures, the unstimulated number of T-lymphoblast colonies (referred to on the ordinate as colonies) formed in incubation mixtures without added insulin is defined as 100%, and the abscissa represents the concentration of added insulin (pM × 10^3). The data are presented as means ± SE.

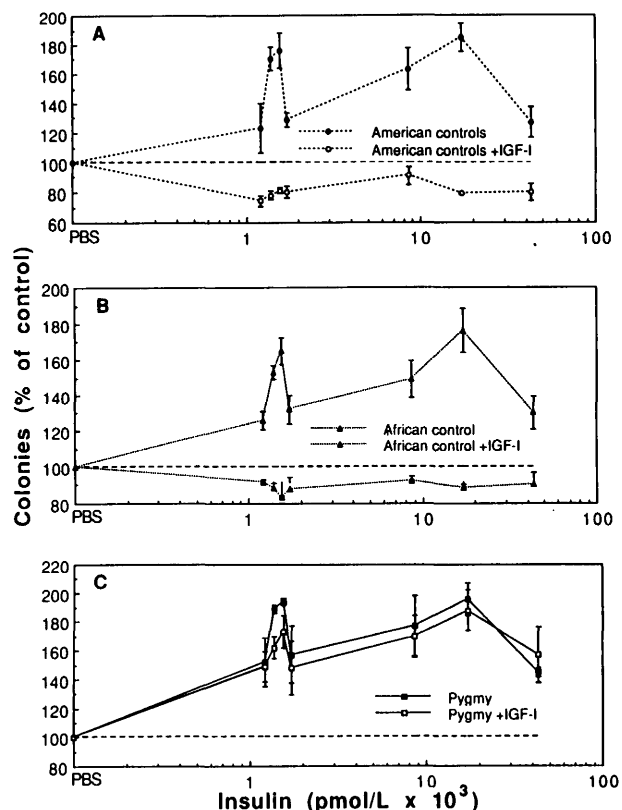

FIG. 2. Insulin responsiveness after IGF-I preincubation; Experimental conditions were identical to those in Fig. 1, which used GH, except that cells were preincubated with recombinant human IGF-I (8 μg/L). *A*: Clonal responsiveness to insulin of American control T-cell lines was completely abrogated after preincubation with IGF-I. *B*: Clonal responsiveness to insulin of the African control T-cell line was also completely blocked after preincubation with IGF-I. *C*: Clonal responsiveness to insulin of the Pygmy T-cell line, however, was not significantly reduced after preincubation with IGF-I.

T-cell lines ($P = 0.97$). The mean first peak response to insulin was 76 ± 11.8% above baseline, and the mean second peak was 85 ± 9.7% above baseline for American control T-cell lines (Fig. 2*A*). For the African control T-cell line, the mean first peak was 65 ± 7.4% above baseline, and the mean second peak was 76 ± 13.3% above baseline (Fig. 2*B*). For the Pygmy T-cell line, the mean first peak was 94 ± 2.2% above baseline, and the mean second peak was 96 ± 11.3% above baseline (Fig. 2*C*). Preincubation of control T-cell lines with IGF-I completely blocked clonal responsiveness to all insulin concentrations studied (American $P = 0.0007$ [Fig. 2*A*] and African $P = 0.001$ [Fig. 2*B*], respectively, versus no IGF-I). After preincubation of the Pygmy T-cell line with IGF-I, no significant change was observed in overall responsiveness to insulin ($P = 0.74$ versus no IGF-I); the mean first peak response was 73 ± 11.0% above baseline, and mean second peak was 88 ± 13.8% above baseline (Fig. 2*C*).

Insulin responsiveness of normal T-cell lines after αIR-3 and either GH or IGF-I preincubation. As above, GH significantly reduced clonal responsiveness of American control T-cell lines to all concentrations of insulin ($P = 0.003$ versus insulin alone). Under conditions of combined preincubation with GH and αIR-3, the profile of clonal responsiveness to insulin normalized ($P = 0.26$ versus insulin alone [Fig. 3*A*]). As above, IGF-I significantly reduced clonal responsiveness to all concentrations of insulin ($P = 0.007$ versus insulin alone). Under conditions of combined preincubation with IGF-I and αIR-3, the profile of clonal responsiveness to insulin normalized ($P = 0.91$ versus insulin alone [Fig. 3*B*]).

DISCUSSION

We have shown previously that basal colony formation of normal T-lymphoblasts is augmented in response to direct stimulation with GH, IGF-I, and insulin (11,13). The ability of GH to increase basal colony formation of normal T-lymphoblasts appears to be mediated by local production, secretion, and action of IGF-I. Although GH failed to produce significant increases in IGF-I levels in condi-

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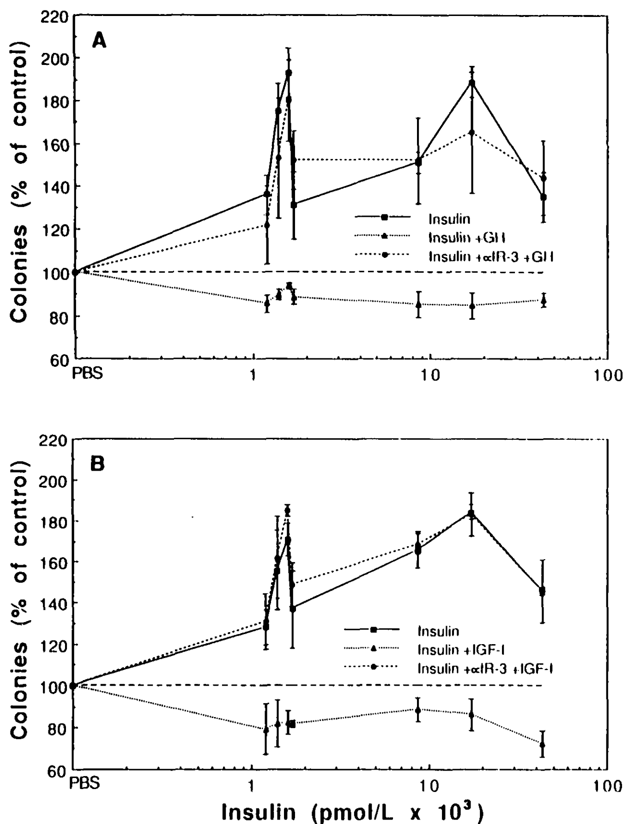

FIG. 3. Insulin responsiveness of normal T-cell lines after IGF-I receptor antibody and either GH or IGF-I preincubation. T-cell line clonal responses to insulin after either GH or IGF-I preincubation were quantified in the presence or absence of αIR-3, as described in METHODS. The αIR-3 was added 1 h before GH or IGF-I preincubation at a final concentration of 5×10^{-4} g/L. *A*: As in Fig. 1*B*, GH significantly reduced clonal responsiveness of American control T-cell lines to all concentrations of insulin. Under conditions of combined preincubation with GH and αIR-3, the profile of clonal responsiveness to insulin normalized. *B*: As in Fig. 2*B*, IGF-I significantly reduced clonal responsiveness of American control T-cell lines to all concentrations of insulin. Under conditions of combined preincubation with IGF-I and αIR-3, the profile of clonal responsiveness to insulin normalized.

tioned media, the clonal proliferative response to GH could be abrogated by pretreatment with antibody to either the IGF-I receptor or to IGF-I itself (14). In separate experiments, we have also shown that GH preincubation of normal T-lymphoblasts induces complete resistance to subsequent mitogenic stimulation by insulin at concentrations ranging from 1.2 to 43.2×10^3 pM (6). In this study, we examined the role of local IGF-I in the mediation of GH-induced resistance to the mitogenic action of insulin. In addition to using normal T-cell lines in the context of the current experiments, we also studied an immortalized T-cell line from an African Pygmy because of its resistance to the direct, growth-promoting actions of both IGF-I and GH (7). We have determined that the resistance in the Pygmy was attributable to a variation in the ability of Pygmy cells to bind IGF-I (7). Our findings confirm that GH preincubation of normal American and African T-cell lines induces resistance to the mitogenic action of insulin and indicate, for the first time, that this effect requires the local action of IGF-I. In contrast, with the Pygmy T-cell line, neither GH nor IGF-I preincubation induces resistance to subsequent mitogenic stimulation by insulin, presumably because of a nonfunctional IGF-I receptor.

Insulin concentrations $>1.7 \times 10^3$ pM stimulate colony formation of normal T-cell lines through the IGF-I receptor, because this effect can be completely abrogated by preincubation with αIR-3 (11). Although the Pygmy T-cell line does not bind or respond to physiological concentrations of IGF-I, it does respond normally to high insulin concentrations, an effect which was not significantly blocked by preincubation with αIR-3 (7). Thus, there must be a pathway independent of the type-I IGF receptor in the Pygmy T-cell line that mediates the growth-promoting action of supraphysiological concentrations of insulin. Formation of hybrid insulin-IGF-I receptors (15) that can respond to insulin, but not to IGF-I, is one mechanism that could explain these results.

The actions of GH can be divided into two general categories: anabolic and metabolic. It is well accepted that the anabolic or growth-promoting actions of GH are indirect. This led to the development of the original somatomedin hypothesis (16), which stated that the effects of GH on somatic growth were not attributable to direct action of GH; instead, they were mediated by IGF-I, which was synthesized in nonskeletal tissue, i.e., the liver. More recently, GH has been shown to regulate the production of IGF-I by many tissues that lead to a modification of the original hypothesis to include autocrine and paracrine actions of IGF-I in the promotion of local tissue growth (17). In either case, IGF-I appears to confer the growth-promoting actions of GH.

GH also has multiple metabolic actions, some of which are insulin-like and most of which are insulin-antagonistic (2). The insulin-like effects of GH appear within a few minutes of GH administration, are maximal at 1 h, and gradually abate over the next 1–2 h (4). Once these effects of GH dissipate, re-exposure to GH fails to elicit similar insulin-like actions for many hours, although adipose tissue remains responsive to insulin and IGF-I (18,19). Because similar exposure of 3T3-F442 adipocytes to IGF-I leads to insulin-like effects that are neither transient nor subject to refractoriness, it is unlikely that these insulin-like metabolic actions of GH are attributable to locally produced IGF-I (20). With longer exposure times to GH, insulin-antagonistic effects (e.g., lipolysis) become apparent. The insulin-antagonistic action of GH on normal adipose tissue does not appear to be mediated by IGF-I because similar degrees of lipolysis were induced by combined in vitro dexamethasone and GH treatment in the presence and absence of a monoclonal antibody to IGF-I itself (4).

It should be emphasized that the insulin resistance we observed after GH preincubation of normal T-cell lines reflects resistance to the mitogenic action of insulin. Studies of mutant insulin receptors suggest that there are at least two transduction systems that separately regulate the cellular growth-promoting and metabolic actions of insulin (21). Interestingly, in the human model of acromegaly, it has been shown that there is a negative correlation between in vivo insulin sensitivity—as measured from the continuous infusion of glucose with model

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assessment (CIGMA)—and circulating serum IGF-I, but not GH, concentrations (22). Our data do not address the effects of in vitro GH preincubation on the metabolic actions of insulin.

Our finding that neither GH nor IGF-I preincubation of the Pygmy T-cell line induced resistance to the mitogenic action of insulin provides a second line of evidence that this Pygmy T-cell line is resistant to both GH and IGF-I. We indicated previously that this Pygmy T-cell line showed no clonal stimulation in response to direct stimulation with physiological concentrations of either GH, IGF-I, or the IGF-I analog [Q^3,A^4,Y^{15},L^{16}]IGF-I, which binds to the type-I IGF receptor, but not to IGF-binding proteins, as well as no specific IGF-I binding (7). These findings led us to propose that IGF-I resistance was the underlying variation in the Pygmy, with GH resistance secondary. The absent binding of IGF-I to the Pygmy cells confirmed an IGF-I receptor variation as the underlying pathophysiological mechanism of GH and IGF-I nonresponsiveness. These findings are not inconsistent with previous data that implicates GH resistance as the cause for the growth disorder of Pygmies (23). For example, perhaps short-term GH treatment of adult Pygmy subjects failed to induce characteristic metabolic effects (24) because IGF-I is needed to mediate these in vivo actions of GH. Furthermore, the diminished proliferation of Pygmy Epstein–Barr–virus-transformed B-lymphocyte cell lines after GH stimulation (25) may be explained by blunted local secretion of IGF-I combined with resistance to this secreted IGF-I.

In conclusion, we have shown that either GH or IGF-I preincubation of normal T-cell lines significantly blunts mitogenic responsiveness to subsequent stimulation with insulin, effects that can be blocked by pretreatment with an antibody against the IGF-I receptor. These data suggest that local IGF-I mediates GH-induced resistance to the mitogenic action of insulin. Additionally, we found that neither GH nor IGF-I preincubation induces resistance to the growth-promoting action of insulin in a Pygmy T-cell line. This is a second line of evidence showing that this Pygmy T-cell line is IGF-I-resistant, which we believe is the underlying variation responsible for the short stature that characterizes this population.

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