Metabolic Effects of Insulin-Like Growth Factor-I: A Focus on Insulin Sensitivity

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THE TERM INSULIN-LIKE growth factor (IGF) was introduced by Rinderknecht and Humbel in 1978.[1] They had isolated two peptides (IGF-I and IGF-II) from human serum that are structurally homologous to proinsulin. IGF-I shares approximately 45% sequence homology with the A and B chains of insulin, suggesting that IGFs and insulin may have evolved from a common precursor gene. Apart from the structural homology to insulin, IGF-I shares considerable biological activities with insulin.

Cellular actions of IGF-I are mediated by the type 1 IGF receptor, which is homologous to the insulin receptor with an $\alpha_2\beta_2$ heterotetrameric structure and a tyrosine kinase in the intracellular portion of the β-subunits. The type 2 IGF receptor is identical to the mannose-6-phosphate receptor. Due to the similarities in ligand and receptor structures, it is not surprising that both insulin and IGF-I can cross-react with each other's receptor, but with a 10- to 100-fold reduced affinity as compared with binding to their own respective receptors. It is important to note that in rodents and man, tissue distributions of insulin and type 1 IGF receptors are considerably different. Whereas hepatocytes and adipocytes are classic target tissues for insulin, they lack functional receptors for IGF. Skeletal muscle carries both insulin and type 1 IGF receptors.[2]

Circulating IGF-I is mainly synthesized in the liver. Synthesis of IGF-I is regulated by several factors. Growth hormone (GH) stimulates synthesis and secretion of hepatic IGF-I.[3] IGF-I, in turn, regulates pituitary GH secretion by feedback inhibition.[4,5] IGF-I synthesis is also supported by insulin. Lack of insulin, as in type I diabetics, is accompanied by reduced insulin and IGF-I levels, although GH secretion is elevated.[6-8] Fasting is accompanied by reduced circulating IGF-I levels (despite elevated GH secretion and during reduced insulin secretion), which are normalized upon refeeding.[9]

In the following sections, the metabolic effects of IGF-I are summarized, with special reference to IGF-I effects on insulin sensitivity.

INTRAVENOUS ADMINISTRATION OF IGF-I

An acute intravenous bolus administration of IGF-I to rats[10] and humans[11] leads to hypoglycemia similar to that seen after insulin injection. The hypoglycemic potency of IGF-I is approximately 10 to 13 times less than that of insulin. Infusions of IGF-I, like insulin, also lead to reduced protein degradation, as reflected by reduced amino acid levels,[12,13] and to reduced oxidative leucine disposal.[14,15]

Whereas bolus administrations of IGF-I and insulin lead to identical changes, infusions of these hormones during several hours in humans show distinct differences between insulin and IGF-I. At identical rates of glucose assimilation, IGF-I is relatively more potent in stimulating peripheral glucose disposal and less effective in inhibiting hepatic glucose production.[16] IGF-I infused intravenously at a dose that clearly stimulates glucose uptake does not suppress lipolysis.[17] In contrast, insulin infused at a dose that produces similar glucose uptake rates as IGF-I already has profound inhibitory effects on lipolysis. The differences between IGF-I and insulin, mainly seen during administration of relatively low IGF-I doses, are mostly due to differences in tissue distribution of the insulin and type 1 IGF receptors. Hepatocytes and adipocytes lack functional receptors for IGF-I. Thus, IGF-I has no effects on hepatic glucose production or lipolysis at low doses, and exerts it effects on these tissues at high doses only by cross-reaction with the insulin receptor.[18-21]

EFFECTS OF IGF-I ON GH, INSULIN, AND GLUCAGON SECRETION

During treatment with IGF-I, spontaneous GH secretory pulses are blunted. Moreover, IGF-I treatment leads to reduced GH secretion after stimulation with GH-releasing hormone[4] or L-arginine infusions[22] and during hypoglycemia induced either by IGF-I[23] or by insulin administration in addition to IGF-I treatment (Hussain MA, et al, unpublished results).

Apart from inhibiting GH secretion, IGF-I also suppresses insulin secretion. This has been demonstrated in the isolated perfused rat pancreas[24] and in vivo in humans.[11,25] Moreover, IGF-I administration for several days is accompanied by reduced insulin secretion, despite the fact that glucose levels and glucose turnover remain unchanged[22] (Fig 1). When healthy volunteers treated with IGF-I receive an intravenous glucose bolus, their glucose tolerance is identical to that seen in the control situation. Although insulin secretion is reduced during IGF-I treatment, the insulin response to a glucose challenge is prompt[22] (Fig 2). This fact would be important for the therapeutic use of IGF-I, allowing an adequate and prompt insulin secretory response of pancreatic β cells during meal intake.

When infused acutely, IGF-I also suppresses glucagon secretion.[12] However, after a 5-day IGF-I treatment, basal glucagon levels and L-arginine–stimulated glucagon secretion are unchanged.[22] Inhibitory effects of IGF-I on the secretion of GH, insulin, and glucagon are most likely direct via receptor-mediated effects of IGF-I on the respective endocrine cells. Type 1 IGF-I receptors have been demon-

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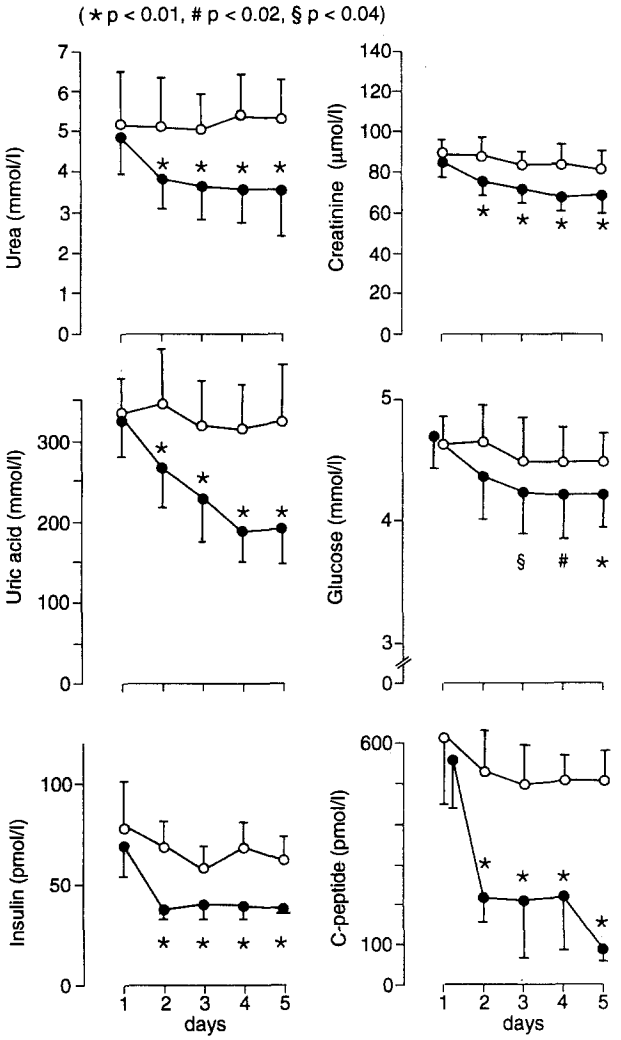

Fig 1. Metabolic parameters in 8 healthy subjects during a 5-day treatment with IGF-I (10 μg/kg · h subcutaneously [SC]) and saline. (Reprinted from the *Journal of Clinical Investigation* 92:2249-2256, 1993[22] by copyright permission of the American Society for Clinical Investigation.

strated on GH-producing pituitary cells,[5] as well as on pancreatic α and β cells.[26]

Since IGF-I is considered a potential therapeutic agent in diabetes, responses of other counterregulatory hormones to hypoglycemia during IGF-I administration have also been thoroughly investigated. Cortisol and norepinephrine secretion remain unaffected during IGF-induced hypoglycemia and during insulin-induced hypoglycemia in IGF-I–treated man[23] (Hussain MA, et al, unpublished results).

METABOLIC EFFECTS OF SHORT-TERM TREATMENT WITH IGF-I IN HUMANS: SUBSTRATE METABOLISM

When healthy subjects are treated with IGF-I and substrate metabolism and energy expenditure are assessed by indirect calorimetry, a 10% to 20% increase in basal metabolic rate is observed. These changes are accompanied by enhanced lipid oxidation, while protein oxidation is reduced and basal glucose metabolism remains unchanged.[22]

Similar changes in substrate oxidation are found in IGF-I–treated, GH-deficient adults[27] (Fig 3). Moreover, the changes in energy expenditure and substrate combustion are similar to those observed during GH treatment of healthy or GH-deficient adults.[28] When GH and IGF-I are administered together to GH-deficient subjects, both hormones have synergistic effects on energy expenditure and on substrate oxidation rates[27] (Fig 3).

Treatment with GH or IGF-I is accompanied by enhanced lipolysis (liberating free fatty acids, which then serve as fuels for the enhanced energy expenditure). However, the mechanism by which GH and IGF-I induce these changes are different. Whereas GH directly induces lipolysis in adipose tissue, leading to increased circulating free fatty acid levels, IGF-I has no direct effects on adipocytes due to the lack of functional receptors. Most likely, IGF-I enhances lipolysis by reducing insulin levels and thus releasing the brakes on lipolysis. GH as well as IGF-I treatment is accompanied by reduced proteolysis (probably in skeletal muscle). Whether these effects are mediated by

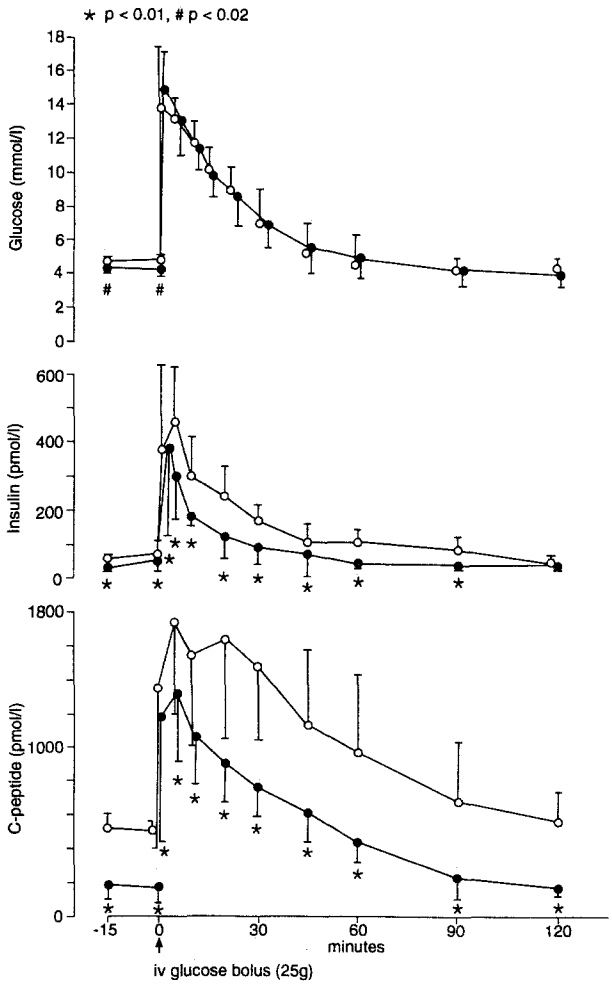

Fig 2. Insulin response to an intravenous glucose tolerance test in healthy subjects during treatment with IGF-I (10 μg/kg · h SC) and saline. Reprinted from the *Journal of Clinical Investigation* 92:2249-2256, 1993[22] by copyright permission of the American Society for Clinical Investigation.

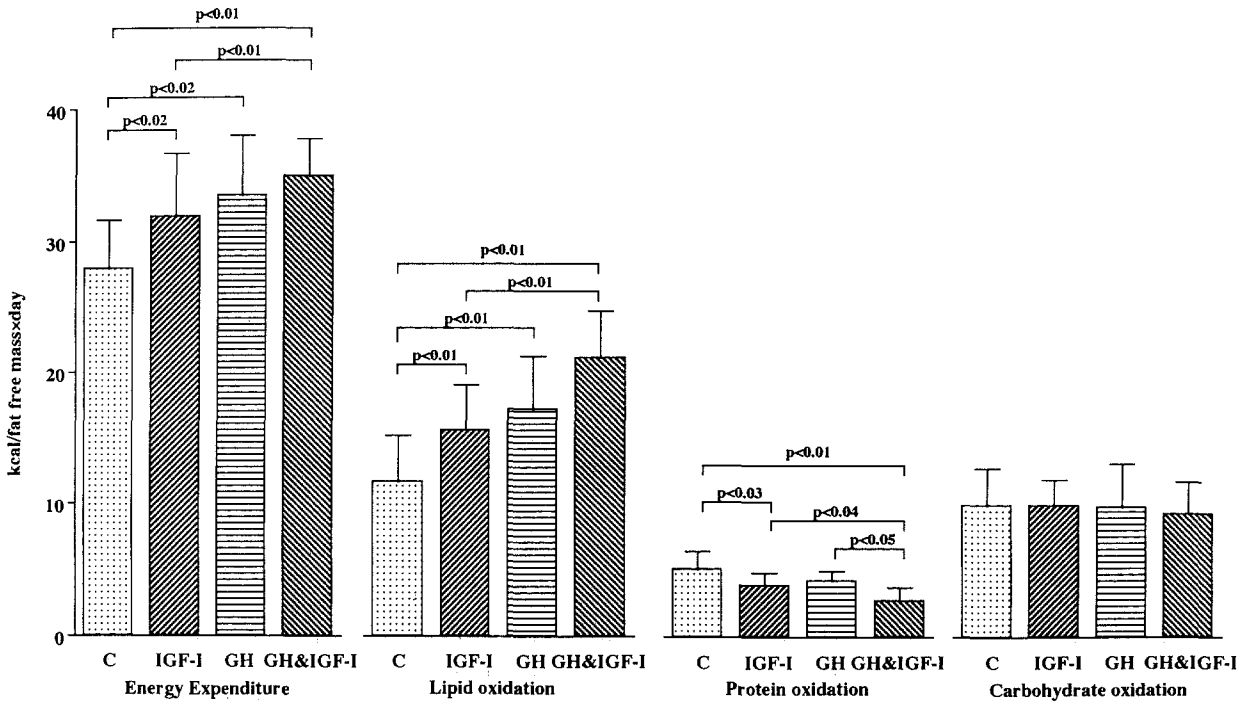

Fig 3. Substrate oxidation rates in 8 GH-deficient subjects during control (C) conditions and treatment with IGF-I (10 μg/kg · h SC), GH (2 IU/m² · d SC), and GH + IGF-I for 7 days each. Reprinted from the *Journal of Clinical Investigation* 94:1126-1133, 1994[27] by copyright permission of the American Society for Clinical Investigation.

IGF-I or whether GH also directly influences protein metabolism in skeletal muscle is unknown.

Enhanced energy expenditure during GH and IGF-I treatment is not merely due to enhanced availability of lipids for fuel combustion, but rather to a direct anabolic effect of these hormones. GH treatment in GH-deficient adults only transiently leads to enhanced energy expenditure, accompanied by elevated lipid mobilization and combustion, before energy expenditure and fuel homeostasis stabilize at a new steady state in body composition.[29] As yet, no such data are available for IGF-I.

EFFECTS OF IGF-I ON INSULIN SENSITIVITY

Resistance to the effects of insulin is considered an early step in the pathogenesis of type II diabetes mellitus. Several strategies have been proposed to counteract the insulin resistance. In this regard, IGF-I may be one of the potential therapeutic options.

Oral glucose and meal tolerance remain unchanged during IGF-I treatment, despite a dose-dependent reduction of basal and stimulated insulin secretion.[30] This phenomenon was interpreted as an insulin-sparing effect of IGF-I. Indeed, a 5-day IGF-I treatment of healthy volunteers leads to increased insulin sensitivity as assessed by the euglycemic, hyperinsulinemic clamp method.[22] Increased insulin sensitivity may be caused by several mechanisms: (1) direct effects of IGF-I on insulin target tissues, (2) indirectly through reduced GH secretion (GH induces insulin resistance),[31] and (3) via reduction of insulin levels, leading to an upregulation of insulin receptors and thereby to increased insulin sensitivity.[32]

In GH-deficient subjects, GH treatment induces insulin resistance, whereas IGF-I treatment improves insulin sensitivity. IGF-I given on top of GH treatment partially reverses the insulin resistance induced by GH.[27,33] These data may be interpreted to mean that IGF-I also exerts a direct effect on insulin sensitivity (mainly of skeletal muscle tissue) that is independent of the reduction of GH levels seen during IGF-I treatment of healthy adults.

Insulin sensitivity is diminished in elderly subjects as compared with younger counterparts. Interestingly, the sensitivity to the hypoglycemic effects of IGF-I does not wane with age.[34]

IGF-I FOR TREATMENT OF DIABETES MELLITUS

IGF-I has been considered as a potential therapeutic agent for treatment of diabetes mellitus because of its effects on glucose metabolism and insulin sensitivity. Several preliminary reports have provided encouraging results.

Insulin-Dependent Diabetes Mellitus

IGF-I treatment led to reduced basal and mealtime insulin requirements (up to 50%) in two isocalorically fed adults with insulin-dependent diabetes mellitus.[35]

Adolescents with insulin-dependent diabetes mellitus who have relatively low IGF-I serum levels were treated with substitution doses of IGF-I for 4 weeks. They needed less insulin, and their metabolic control was improved. These effects were mainly attributed to reduced nocturnal GH secretion, leading to a blunting of the so-called dawn phenomenon.[36]

Non–Insulin-Dependent Diabetes Mellitus

As noted, insulin sensitivity is improved during IGF-I treatment. These observations are encouraging for the treatment of patients with non–insulin-dependent diabetes mellitus, whose insulin sensitivity is typically reduced in the face of elevated insulin levels, subsequently disturbed lipid metabolism, and hypertension (metabolic syndrome).[37]

Short-term treatment with IGF-I in slightly obese type II diabetics reduced insulin levels and improved metabolic control.[38] Oral glucose tolerance and meal tolerance were improved in these patients despite reduced insulin secretion. Side effects were limited to an asymptomatic increase in heart rate of up to 10%, slight parotid tenderness, and slight subcutaneous edema. All of these side effects were reversible after termination of IGF-I treatment.

Other investigators have reported severe side effects of IGF-I treatment in obese type II diabetics. However, IGF-I was clearly overdosed in these subjects, since dosage was not adjusted to ideal body weight.[39,40]

Extreme Insulin Resistance

Type A insulin resistance results from either mutations in the insulin receptor gene or defects at critical postreceptor sites.[41] Patients with type A insulin resistance are characterized by impaired glucose tolerance or frank diabetes despite elevated insulin levels. Insulin, even in excessive doses, does not improve metabolic control in these patients.

Intravenous bolus injections of recombinant human IGF-I resulted in a normalization of hyperglycemia within 6 to 8 hours in two patients with type A insulin resistance.[42] Whereas hypoglycemia after an intravenous bolus of IGF-I develops in healthy subjects as rapidly as after intravenous insulin, blood glucose in type A insulin-resistant patients decreases at a significantly slower rate. One may speculate that the IGF-I effects were transmitted by the type 1 IGF-I receptor only and not by cross-reaction of IGF-I with the nonfunctional insulin receptor.

During a 5-day treatment of type A insulin-resistant patients with IGF-I, fasting glucose levels were normalized and postprandial glucose metabolism was improved.[43,44] In a multicenter study conducted in Japan, 15 type A diabetic subjects were treated with IGF-I over a period of several weeks. IGF-I substantially improved glucose control. Side effects were not reported in this study.[45]

Not all insulin-resistant subjects respond with improved metabolic control during IGF-I treatment.[46] Since the molecular defects leading to the type A insulin resistance syndrome are heterogeneous, the response of affected patients to IGF-I therapy may vary considerably. Not all patients with insulin resistance may benefit from this form of therapy.

It is important to note that IGF-I treatment in normal subjects always leads to changes in levels of IGF-binding proteins[47,48] (and R.C. Baxter in this issue). These changes in IGF-binding protein levels are important for the understanding of in vivo effects of exogenously administered IGF-I, which may not merely reflect the physiological effects of endogenously synthesized IGF-I.

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