Low-dose IGF-I has no selective advantage over insulin in regulating glucose metabolism in hyperglycemic depancreatized dogs

S J Fisher1, Z Q Shi1,2, H L Lickley1,2, S Efendic4, M Vranic1,3 and A Giacca1,3

1Department of Physiology, University of Toronto, Toronto, Ontario, Canada
2Department of Surgery, University of Toronto, Toronto, Ontario, Canada
3Department of Medicine, University of Toronto, Toronto, Ontario, Canada
4Department of Endocrinology, Karolinska Hospital, Stockholm, Sweden

Abstract

At supraphysiological levels, IGF-I bypasses some forms of insulin resistance and has been proposed as a therapeutic agent in the treatment of diabetes. Unfortunately, side effects of high-dose IGF-I (100–250 µg/kg) have precluded its clinical use. Low-dose IGF-I (40–80 µg/kg), however, shows minimal side effects but has not been systematically evaluated. In our previous study under conditions of declining glucose, low-dose IGF-I infusion was more effective in stimulating glucose utilization, but less effective in suppressing glucose production and lipolysis than low-dose insulin. However, under conditions of hyperglycemia, we could not observe any differential effects between high-dose infusions of IGF-I and insulin. To determine whether the differential effects of IGF-I and insulin are dose-related or related to the prevailing glucose level, 3 h glucose clamps were performed in the same animal model as in the previous studies, i.e. the moderately hyperglycemic (175 mg/dl) insulin-infused depancreatized dog, with additional infusions of low-dose IGF-I (67·8 µg/kg, i.e. 29·1 µg/kg bolus plus 0·215 µg/kg per min infusion; n=5) or insulin 49·5 mU/kg (9 mU/kg bolus plus 0·45 mU/kg per min; n=7). As in the previous study under conditions of declining glucose, low-dose IGF-I had significant metabolic effects in vivo, in our model of complete absence of endogenous insulin secretion. Glucose production was similarly suppressed with both IGF-I and insulin, by 54 ± 3 and 56 ± 2% s.e. (P=NS) respectively. Glucose utilization was stimulated to the same extent (IGF-I 5·2 ± 0·2, insulin 5·5 ± 0·3 mg/kg per min, P=NS). Glucagon, free fatty acid, glycerol, alanine and beta-hydroxybutyrate, were suppressed, while lactate and pyruvate levels were raised, similarly with IGF-I and insulin. We conclude that: (i) differential effects of IGF-I and insulin may be masked under hyperglycemic conditions, independent of the hormone dose; (ii) low-dose IGF-I has no selective advantage over additional insulin in suppressing glucose production and lipolysis, nor in stimulating glucose utilization during hyperglycemia and subbasal insulin infusion when insulin secretion is absent, as in type 1 diabetes mellitus.

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Introduction

Insulin–like growth factor-I (IGF-I) is structurally similar to insulin and at pharmacological doses can mimic many of the effects of insulin on carbohydrate, lipid and protein metabolism. The stimulatory effect of IGF-I on glucose metabolism had prompted interest in its possible therapeutic use as an adjuvant treatment of diabetes. Unfortunately, high doses of IGF-I in the range of 100–250 µg/kg and up to 500 µg/kg administered either i.v. or s.c. have been associated with adverse side effects (Schalch et al. 1993, Jabri et al. 1994, Usala et al. 1994, Moses et al. 1996). Minor side effects include weight gain, facial and hand edema and temporomandibular tenderness; more serious side effects include symptomatic hypoglycemia, Bell’s palsy, acromegaloid features, increased intracranial pressure, gynecomastia and avascular necrosis of the femur (reviewed in Bondy et al. 1994 and Malozowski & Stadel 1994). There has also been concern regarding the possible contribution of IGF-I to potentiate diabetic complications (Meyer-Schwickerath et al. 1993, Janssen et al. 1997). Recent reports, however, suggest that lower IGF-I doses in the range of 40–80 µg/kg are better tolerated and show minimal or no adverse side effects in diabetic subjects (Bach et al. 1994, RINDS 1996a, b, Acerini et al. 1997, Carroll et al. 1997, Quattrin et al. 1997). Clinical
trials have shown that low-dose s.c. IGF-I (in the range 40–80 µg/kg) can decrease insulin requirements, lower glycated hemoglobin and fasting glycemia, and improve insulin sensitivity in both type 1 (Acerini et al. 1997, Carroll et al. 1997, Quattrin et al. 1997) and type 2 diabetic subjects (Cusi & DeFronzo 1995, RINoS 1996a, b). Unfortunately, the acute metabolic responses to these low doses of IGF-I have been less well characterized. Many of the differential effects of IGF-I vs insulin in acutely stimulating glucose metabolism observed at higher doses (above 100 µg/kg) are not observed at lower doses (Laager et al. 1993, Boulware et al. 1994). Studies comparing metabolic responses to high- and low-dose IGF-I infusion have found that glucose kinetics may not respond in a dose-dependent fashion (Shojaee-Moradie et al. 1995), which may be related to the effects of circulating IGF-binding proteins or variable suppression of endogenous insulin and/or glucagon. Few studies have assessed the acute metabolic responses to low-dose IGF-I administration in diabetic subjects. Cheetham et al. (1993) noted that a single IGF-I dose of 40 µg/kg resulted in a decreased insulin requirement to maintain euglycemia in type 1 diabetic adolescents. Acerini et al. (1997) noted that in response to a single 40 µg/kg injection of IGF-I in type 1 diabetic subjects there were decreased insulin requirements and an increased hepatic insulin sensitivity. To date, a comparison between the acute metabolic responses to low-dose IGF-I and insulin has not been reported in hyperglycemic diabetic subjects. Given the renewed clinical interest in low-dose IGF-I administration with its favorable safety profile, it is important to assess under diabetic conditions whether low-dose IGF-I has any selective advantage over insulin administration (possibly by binding to the IGF-I receptor).

We have previously reported that low-dose IGF-I (67.8 µg/kg) increased glucose utilization and lactate more, and suppressed glucose production (GP) and lipolysis less, than an equipotent dose of insulin under conditions of a glucose decline (Giacca et al. 1990). Equipoverty on whole body glucose metabolism was judged based on the hormone doses required to induce the same lowering of plasma glucose (this required a greater stimulation of glucose utilization but less inhibition of GP with IGF-I than insulin). Since that study suggested that the IGF-I/insulin potency ratio is higher in muscle than liver or adipose tissue, we proposed that some insulin-like effects of IGF-I+insulin could be mediated not only through the insulin receptor, but also through the IGF-I receptor.

We then observed that these differential effects of IGF-I and insulin on glucose regulation were masked when higher doses of IGF-I (>100 µg/kg) and insulin (also equipotent based on similar requirements for exogenous glucose infusion during the glucose clamp) were administered under conditions of maintained hyperglycemia (Giacca et al. 1994). Thus, it was unclear whether the failure to reproduce the differential effects of IGF-I and insulin was dose-related (high-IGF-I doses may cross-react to a greater extent with the insulin receptor than low-IGF-I doses) or dependent on the maintenance of hyperglycemia.

The aim of the present study was to compare the acute metabolic responses of low-dose IGF-I to low-dose insulin administration under conditions of hyperglycemia. The total IGF-I dose was 67.8 µg/kg administered over 3 h (29.1 µg/kg bolus + 0.215 µg/kg per min infusion). As in our previous studies (Giacca et al. 1990, 1994), depancreatized dogs were used as the experimental model, which allowed assessment of IGF-I action on extrapancreatic tissues independent of the insulin suppression effect of IGF-I. In the basal period, steady-state moderate hyperglycemia was maintained by a subbasal intraportal insulin infusion; then an additional infusion of low-dose IGF-I or insulin was administered peripherally. Thus, the experimental design allowed us to compare the effects of IGF-I+insulin to those of insulin alone. Plasma glucose was maintained at the initial hyperglycemic levels with the glucose clamp protocol.

Materials and Methods

Animals

Male mongrel dogs weighing 17–24 kg underwent total pancreatectomy and vessel cannulation under general anesthesia and assisted ventilation, induced with 25 mg/kg thiamylal sodium and maintained with 0.5–1% halothane in carrier gas containing nitrous oxide (2:1:1/min) and oxygen (3:1:1/min). During surgery, silastic cannulae (Dow Corning Corp., Midland, MI, USA) were inserted, (i) into the carotid arch via the carotid artery (0.04 inch internal diameter (i.d.)) for sampling, (ii) into the superior vena cava via the jugular vein (three 0.03 inch i.d. cannulae) for peripheral infusions of tracer and insulin or IGF-I, and (iii) into the portal vein through a branch of the splenic vein (0.04 inch i.d.) for subbasal infusion of insulin. All cannulae were tunneled s.c. and exteriorized at the back of the neck. They were filled with heparin (1000 U/ml, Hepalean; Organon Canada, Toronto, ON, Canada) and were maintained patent by flushing frequently with saline. All procedures were performed in accordance with the Canadian Council of Animal Care standards and were approved by the Animal Care Committee of the University of Toronto. Dogs were fed once daily with a combined diet of 15 g/kg dog chow (Ralston Purina Canada, Mississauga, ON, Canada) and 500 g beef chunks (Canada Packers, Inc., Toronto, ON, Canada). Pancreatic enzymes were supplemented (Cotazyme; Organon). Diabetes was treated with a once daily s.c. injection of regular (4–15 U) and NPH (8–30 U) porcine insulin (Eli Lilly and Company, Indianapolis, IN, USA). Only dogs with at least 5 days of relatively well-controlled diabetes (glycosuria<1%) and the absence of diarrhea and visible steatorrhea were used for experimental studies.
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Experimental protocol

Twelve experiments were carried out in seven conscious dogs 1–6 weeks after pancreatectomy. Insulin was withdrawn for at least 24 h, and food was withdrawn 18 h before experiments. On the day of the study, an intraportal infusion of insulin (3.3 mU/kg per min) was started and gradually reduced until moderate hyperglycemic levels were reached (≈175 mg/dl). These levels were maintained by infusing intraportal insulin at a constant sub-basal rate (0.019 ± 0.05 mU/kg per min). This constant intraportal insulin infusion was maintained throughout the experiment. In depancreatized dogs, it is not necessary to infuse glucagon, as the dog’s stomach mucosa secretes normal amounts of glucagon that compensate for the lack of pancreatic glucagon. When plasma glucose decreased below 250 mg/dl, a primed (70 mCi) continuous infusion (0.5 mCi/µCi/min) of HPLC-purified 50% tracer mixture of [2-3H]- and [6-3H]glucose (New England Nuclear, Boston, MA, USA) was started and continued for at least 120 min for tracer equilibration before the 30 min basal blood sampling period. At time = 0, either human recombinant IGF-I (KabiPharmacia Peptide Hormones, Stockholm, Sweden) or insulin prepared in a saline vehicle containing approximately 4% (v/v) of the dog’s plasma was administered peripherally through a separate catheter. The total dose of IGF-I was 67.8 µg/kg (29.1 µg/kg bolus plus 0.215 µg/kg per min; n = 5) and the total dose of insulin was 49.5 µg/kg (9 µU/kg bolus plus 0.45 mU/kg per min; n = 7) each infused for 180 min. On a molar basis, the dose of IGF-I was 12.2 higher than that of insulin. This low dose of IGF-I was within the 40–80 µg/kg range shown to be well tolerated in clinical trials (RINDS 1996a). Equal potency of the hormone doses on whole body glucose metabolism was chosen based on previous studies (Giacca et al. 1990, 1994) and pilot experiments, which showed similar steady-state glucose requirements with IGF-I/insulin. During the infusion of IGF-I or insulin, plasma glucose was clamped at the initial hyperglycemic levels by adjusting the glucose infusion (Dextrose 50% (w/v); Abbott, Montreal, PQ, Canada), step-wise, based on the results of plasma glucose determinations obtained every 5 min. An aliquot of the 50% tracer mixture was added to the glucose infusate in order to minimize changes in plasma glucose specific activity during the experiment (Fisher et al. 1996). The specific activity of the glucose infusate (SA_Ginf) was calculated based on estimations of the parameters in Finegood’s formula (Finegood et al. 1988), modified to allow for incomplete suppression of GP (Giacca et al. 1992): SAGinf= I.[(Ginf ss/Rab) − F]/(Ginf ss/BW), where SAGinf is the specific activity of glucose infusate, I is the constant tracer infusion rate, Ginf ss is the steady-state glucose infusion rate, Rab is the basal rate of appearance of glucose, BW is the body weight, F (fractional suppression) = (Rab − Rss)/Rab, and Rss is the steady-state endogenous GP. The following initial estimates were employed: Rab = 3.5 mg/kg per min, Rss = 0.5 Rab, Ginf ss = 4 mg/kg per min. Rab was the mean basal GP under identical basal conditions (Giacca et al. 1992, 1994), Rss, and Ginf ss were estimated from pilot experiments.

Blood samples for plasma glucose specific activity were taken every 10 to 15 min, and blood samples for metabolites and hormones every 20 to 30 min.

Laboratory assays

Plasma glucose concentration was measured in duplicate using a Beckman Glucose Analyzer 2 (Beckman, Fullerton, CA, USA). The RIA for total IGF-I in serum (coefficient of variation 10%) was performed on samples extracted with acid–ethanol and using a polyclonal antibody. Insulin and glucagon were assayed by RIA (coefficient of variation, 12 and 15% respectively); free fatty acid (FFA) by a radiochemical technique; and lactate, pyruvate, alanine, glycerol and beta-hydroxybutyrate by enzymatic fluorometric methods as described previously (Giacca et al. 1990).

For determination of [2-3H]- and [6-3H]glucose specific activities, centrifuged plasma was deproteinized with Ba(OH)2 and ZnSO4, and passed through anion and cation exchange resins (Ag 2-X8 and Ag 50W-X8; Bio-Rad Laboratories, Richmond, CA, USA) to remove labeled glucose metabolites. An aliquot of the eluate was then evaporated to dryness to eliminate tritiated water and counted for total radioactivity of both [6-3H]- and [3-3H]glucose. The radioactivity of [6-3H]glucose was determined with the didepen precipitation technique (Dunn et al. 1957). The radioactivity of [2-3H]glucose was calculated as the difference between total radioactivity and that of [6-3H]glucose, corrected for recovery (98 ± 1%). Aliquots of the infused mixture of [6-3H]- and [2-3H]glucose and of the labeled glucose infusate were assayed together with the plasma samples.

Calculations

GP and glucose output were calculated as the endogenous rate of appearance measured with [6-3H]glucose and [2-3H]glucose respectively; glucose cycling was calculated from the difference between glucose output and production; glucose utilization was calculated as the rate of disappearance measured with [6-3H]glucose (Rd). A modified one-compartment model was used to account for the exogenously infused mixture of labeled and unlabeled glucose (Finegood et al. 1988). With this method, the monocompartmental assumption becomes minor because the non-steady-state component of Steele’s equation is close to zero. Data were smoothed according to the ‘optimal-segments method’ (Finegood & Bergman 1983). Rd corresponds to glucose utilization, and plasma clearance rate of glucose (Rd/glycemia) to glucose
metabolic clearance rate because plasma glucose levels were below the renal threshold for glucose in dogs (Bjorkman et al. 1988). During the clamp, exogenous glucose infusion (Ginf) was subtracted from the total rate of glucose appearance to solve for endogenous GP.

Statistical analysis

Statistical analysis was performed with the Statistical Analysis System (SAS, Cary, NC, USA) package on an IBM compatible personal computer. ANOVA for repeated measurements was used to test for differences between experimental groups during two experimental periods (basal: from −30 to 0 min, and clamp: from 0 to 180 min). In addition, where indicated, values for the two treatment groups are compared during the first and last hours of the clamp. ANOVA was also carried out to test for differences between experimental periods (basal and clamp) for each of the two treatments. Data are expressed as means ± s.e. and unless otherwise noted, significance was presumed at \( P<0.05 \).

Results

In the basal period during subbasal portal insulin infusion but before any peripheral hormone infusion, insulin levels were similar at 6.6 ± 0.5 and 7.8 ± 0.4 µU/ml for both the insulin and IGF-I groups respectively (Fig. 1, top panel). With peripheral insulin infusion during the clamp, insulin levels rose 4-fold. With IGF-I infusion, insulin levels remained at basal levels, indicating that IGF-I has no effect on insulin clearance (the portal insulin infusion was continued during the clamp). In the basal period, the IGF-I levels were not significantly different for the insulin and IGF-I treated groups (Fig. 1, middle panel). In response to insulin infusion, the IGF-I levels declined during the clamp (\( P<0.05 \)). In spite of the bolus of IGF-I given, the IGF-I levels rose only gradually, becoming significantly greater than basal levels (\( P<0.01 \)) only during the last 2 h of the clamp. In the basal period before any peripheral hormone infusion, plasma glucagon levels were similar. During the clamp, glucagon levels (Fig. 1, bottom panel) fell (\( P<0.05 \)) similarly with both insulin and IGF-I treatments.

The subbasal infusion of insulin maintained preclamp glycemia constant at 175 ± 3 and 173 ± 1 mg/dl before infusion of insulin or IGF-I (Fig. 2, top panel). During both the insulin and IGF-I infusions, plasma glucose remained clamped (\( P=\)NS, basal vs clamp) at this level of hyperglycemia. The plasma specific activity of [6-\(^3\)H]glucose decreased slightly and similarly with both the insulin (10 ± 2%) by the last hour of the clamp) and IGF-I (16 ± 2%) infusions, but remained within 20% of basal at all times (Fig. 2, middle panel). The fall in [2-\(^3\)H]glucose specific activity also remained within 25% of basal for both treatments (Fig. 2, bottom panel).

The glucose infusion (Fig. 3, top panel) required to maintain glycemia rose briskly during the first hour of the clamp to a greater extent in response to IGF-I vs insulin infusion (3.5 ± 0.4 vs 2.5 ± 0.2 mg/kg per min, \( P<0.05 \)). However, by the last hour of the clamp, glucose infusion
values were similar (insulin $4.2 \pm 0.3$; IGF-I $3.6 \pm 0.3$ mg/kg per min, $P=NS$). GP rates (Fig. 3, middle panel) during the basal period were similar ($3.5 \pm 0.2$ and $3.4 \pm 0.1$ mg/kg per min, $P=NS$, insulin and IGF-I respectively) and were suppressed in a comparable fashion during the clamp ($1.5 \pm 0.1$ and $1.6 \pm 0.1$ mg/kg per min, $P=NS$), which represent suppressions of $56 \pm 2\%$ for insulin and $54 \pm 3\%$ for IGF-I. Glucose output (as measured with [2-3H]glucose; Table 1) was also suppressed equally ($42 \pm 2$ and $40 \pm 2\%$, $P=NS$) with insulin and IGF-I (Table 1). Hepatic glucose cycling (flux between glucose and glucose-6-phosphate), as calculated from the difference between glucose output and production, did not change in response to insulin or IGF-I infusion (Table 1). Glucose utilization (Fig. 3, bottom panel) was similar in the basal period (insulin $3.5 \pm 0.2$; and IGF-I $3.5 \pm 0.1$ mg/kg per min, $P=NS$) and rose significantly higher ($P<0.01$) during the first hour of the clamp with IGF-I ($5.1 \pm 0.2$ mg/kg per min) than with insulin ($4.2 \pm 0.2$ mg/kg per min) infusion, but was similar by the third hour of the clamp (insulin $5.5 \pm 0.3$; and IGF-I $5.2 \pm 0.2$ mg/kg per min, $P=NS$). In a parallel fashion, glucose clearance rates (not shown) were similar in the insulin and IGF-I group in the basal period (2.0 $\pm 0.1$ and 2.0 $\pm 0.1$ ml/kg per min, $P=NS$) and rose higher with IGF-I ($3.0 \pm 0.1$) than insulin ($2.4 \pm 0.1$ ml/kg per min).
min, \( P<0.01 \) during the first hour of the clamp but were similar (insulin 3·1 ± 0·2; and IGF-I 3·0 ± 0·1 ml/kg per min, \( P=\text{NS} \)) by the last hour of the clamp.

Plasma FFA and glycerol levels (Fig. 4, top and middle panels) were similar in the basal period in both insulin and IGF-I groups (FFA: 1190 ± 70 and 1350 ± 150 µM, \( P=\text{NS} \); glycerol: 105 ± 5 and 121 ± 11 µM, \( P=\text{NS} \)) and were suppressed to a similar extent (FFA: 580 ± 50 and 560 ± 50 µM, \( P=\text{NS} \); glycerol: 72 ± 4 and 78 ± 4 µM, \( P=\text{NS} \)) with insulin and IGF-I infusions. Plasma lactate (Fig. 4, bottom panel) was similar in the basal period (700 ± 70 and 740 ± 50 µM, \( P=\text{NS} \), insulin and IGF-I respectively) and increased similarly with insulin and IGF-I infusions (850 ± 50 and 950 ± 34 µM, \( P=\text{NS} \)).

Plasma alanine (Fig. 5, top panel) and beta-hydroxybutyrate levels (Fig. 5, bottom panel) were similar during the basal period and were suppressed to a similar extent during the clamp. Pyruvate levels (Fig. 5, middle panel) were also similar in the basal period in both insulin and IGF-I groups and rose equally during the clamp.

Discussion

Low doses of IGF-I (40–80 µg/kg) are being tested in clinical trials for the treatment of diabetes and other insulin-resistant states (Bach et al. 1994, Cusi & DeFronzo 1995, RINDS 1996a, b, Acerini 1997, Carroll 1997, Quattrin 1997) because high doses of IGF-I (100–250 µg/kg) have been associated with significant adverse side effects (Schalch et al. 1993, Jabri et al. 1994, Usala et al. 1994, Moses et al. 1996). The relative therapeutic efficacy of low-dose IGF-I vs insulin administration has been questioned. We show here that low-dose IGF-I administration (67·8 µg/kg) can significantly suppress GP (54%) and stimulate glucose utilization (49%), and effectively suppress lipolysis in hyperglycemic depancreatized dogs. These low doses of IGF-I, however, have no selective advantage over the administration of low-dose insulin on the acute regulation of glucose turnover and lipolysis.

In this study, there was a much greater bolus-to-infusion ratio for IGF-I than insulin in order to saturate the IGF-binding proteins and attempt to prevent the insulin levels from plateauing much earlier than the IGF-I levels. Despite these efforts, the rise in IGF-I was delayed compared to the prompt rise and plateau seen with insulin administration. Interestingly, it was during this first hour of the clamp when, although there was no detected increase

| Table 1 Glucose output and cycling (mg/kg per min, means ± s.e.) in the basal period and during insulin (n=7) and IGF-I infusions (n=5) |
|-----------------|-----------------|-----------------|-----------------|
|                 | Insulin         | IGF-I           |
|                 | Basal           | 0–180 min       | Basal           | 0–180 min       |
| Glucose output  | 4·8 ± 0·3       | 2·8 ± 0·1*      | 4·4 ± 0·3       | 2·6 ± 0·1*      |
| Glucose cycling | 1·3 ± 0·2       | 1·3 ± 0·1       | 1·0 ± 0·3       | 1·0 ± 0·1       |

\* \( P<0.001 \) 0–180 min vs basal.

Figure 4 Plasma levels of FFA (top panel), glycerol (middle panel) and lactate (bottom panel) before and during IGF-I or insulin infusion. The experimental design is outlined in the legend to Fig. 1. Data are means ± s.e.
in total IGF-I levels, the increment in glucose utilization and glucose infusion was significantly higher for IGF-I than insulin protocols. This suggests that the rapid i.v. bolus of IGF-I increased the free IGF-I levels (not assessed in our assay) over the first hour of the clamp, which allowed for the enhanced stimulation of glucose utilization. Consistent with this hypothesis is the observation that after an i.v. IGF-I bolus, most of the IGF-I remains free and not bound to IGF-binding proteins until 1 h after administration (Zapf et al. 1986). The fact that equal metabolic effects were achieved by only a 2-fold elevation of total IGF-I and a 4-fold elevation of insulin levels is also consistent with the notion that the metabolic effects of IGF-I are determined by the free IGF-I levels.

By experimental design, the doses of IGF-I and insulin were chosen based on their equipotent glucose lowering ability (Giacca et al. 1990). There was a ~50% stimulation of glucose utilization and a ~50% suppression of GP with both hormones. We previously noted that approximately 2-fold higher doses of IGF-I (106.5 µg/kg) and insulin stimulated glucose utilization by ~120% while suppressing GP by ~65% (Giacca et al. 1994). Thus, the stimulation of glucose utilization was linearly dependent on the hormone dose within this range of infusions, whereas the suppression of GP was not. The fact that GP remained as sensitive to the suppressive effects of low-dose IGF-I as that of insulin is somewhat surprising given the paucity of hepatic IGF-I receptors (Caro et al. 1988), but is in accordance with the concept that both IGF-I and insulin may suppress hepatic GP indirectly, i.e. in proportion to peripheral levels, rather than directly, i.e. in proportion to hepatic sinusoidal levels, in hyperglycemic depancreatized dogs. Our previous studies confirm that peripheral insulinemia predominantly determines the suppression of GP in hyperglycemic depancreatized dogs (Giacca et al. 1992, 1999). The mechanism by which peripheral concentrations of insulin and/or IGF-I may suppress GP might be via suppression of glucagon (Giacca et al. 1992, 1997, Lewis et al. 1998), suppression of FFA (Rebrin et al. 1996, Lewis et al. 1997, Sindelar et al. 1997) and gluconeogenic precursors (Giacca et al. 1992, Sindelar et al. 1996). Interestingly, the initial suppression of GP was very rapid, consistent with the IGF-I/insulin bolus being given. An equally rapid suppression of FFA was seen.

We have previously shown that under conditions of equipotency between the two hormones (based on glucose lowering) and declining glycemia, low-dose IGF-I is less effective in suppressing GP but more effective in stimulating glucose utilization than insulin (Giacca et al. 1990). In the present study, the differential effects of IGF-I and insulin were limited to a greater glucose utilization with IGF-I, likely in muscle, and occurred at a time (first hour of the clamp) when IGF-I was more potent than insulin (greater glucose infusion rate), presumably because free IGF-I rose to a greater extent than insulin. However, when IGF-I and insulin were equipotent (same glucose infusion rate), the effects of IGF-I and insulin on GP and utilization were equal. The primary difference between our previous study and our current study is the maintenance of a hyperglycemic state in these depancreatized dogs. Hyperglycemia per se may have masked some of the differential effects between IGF-I and insulin (Giacca et al. 1994). Hyperglycemia can suppress GP (Sacca et al. 1979, Bell et al. 1986) by inhibiting glycogenolysis more than gluconeogenesis (Rossetti et al. 1993). Since insulin’s direct effect on suppressing GP consists primarily of inhibiting glycogenolysis (Sindelar et al. 1996), the
diminished rates of glycogenolysis during hyperglycemia would tend to limit insulin’s direct effects. Therefore, the maintenance of hyperglycemia in the current study may increase the dependence of GP on indirect, peripheral actions of insulin and IGF-I. To support this hypothesis we have recent data suggesting that the acute correction of hyperglycemia can restore the direct or hepatic effect of insulin on GP in depancreatized dogs (Gupta et al. 1998). One could also argue that prevailing level of glycemias could have altered the concentrations of IGF-binding proteins (Baxter 1991). Thus, hyperglycemia may affect IGF-I action by means of regulating IGF-binding protein levels which might account for some of the discrepancies between this study and our previous study (Giacca et al. 1990).

Since a control group (i.e. saline infusion) was not included in this study, it could be argued that some of the changes in metabolites and glucose turnover during the 180 min clamp period may have been due to the prolongation of fasting or the failure to reach steady-state during the 120 min tracer equilibration period. These two sources of variability might confound our results comparing IGF-I and insulin protocols. We have previously addressed these issues with a separate group of depancreatized dogs under identical conditions of hyperglycemia maintained with subbasal intraportal insulin infusions (Fisher et al. 1996). We observed that, consistent with the loss of glucose–insulin feedback in these depancreatized dogs, there was a slight tendency for GP to decrease (less than 20%) although glucose utilization did not change significantly from basal conditions over 180 min in this control group (Fisher et al. 1996). Thus, in the present study we recognize the possibility that a small portion of the 55% GP suppression attributed to insulin or IGF-I administration during the 3 h clamp may in part be due to the prolongation of fasting.

Increased glucose cycling is an early and sensitive indicator of altered hepatic glucose metabolism in type 2 diabetes (Efendic et al. 1988). In this study, low-dose IGF-I or insulin failed to reduce glucose cycling under conditions of hyperglycemia. We have previously shown that the simultaneous correction of both hyperglycemia and hypoinsulinemia may be necessary for the correction of elevated glucose cycling in diabetes (Shi et al. 1994).

The effects of IGF-I on FFA metabolism have been conflicting. High doses of IGF-I have been shown to suppress FFA levels, oxidation and turnover (Guler et al. 1987, Laager et al. 1993, Boulware et al. 1994, Utsala et al. 1994). Given the reduced expression of IGF-I receptors on the adipocyte (Zapf et al. 1981, Sinha et al. 1989), it was speculated that IGF-I suppresses lipolysis via its cross-reactivity with the insulin receptor, thus requiring high IGF-I levels to mediate effects on the adipocyte. Thus, it was somewhat expected when low-dose IGF-I administration was found to have no effect on FFA metabolism (Mauras et al. 1992, Elahi et al. 1993, Laager et al. 1993). In the current study, it was surprising to note that low-dose IGF-I induced suppression of FFA levels by 50% and glycerol by 30%. The reason for the anti-lipolytic effect seen in our low-dose IGF-I study as compared to others may be multifactorial and related to IGF-binding proteins, the disturbed growth hormone–IGF axis, the hyperglycemic state, or our model of diabetes. Indeed, the anti-lipolytic effects of low-dose IGF-I may be revealed in the depancreatized dog due to absence of confounding effects of IGF-I-mediated suppression of endogenous insulin secretion. We speculate that the failure of low-dose IGF-I to demonstrate anti-lipolytic effects in previous studies (Mauras et al. 1992, Elahi et al. 1993, Laager et al. 1993) may be related to conflicts with the lipolytic effects of a concomitant IGF-I-mediated suppression of insulin secretion.

In summary, in our model of type 1 diabetes, similar to our previous study with high-dose IGF-I, low-dose IGF-I had the same effects as additional insulin in suppressing GP and lipolysis and stimulating glucose utilization during hyperglycemia and subbasal insulin infusion. We conclude that: (i) differential effects of IGF-I and insulin are not dose-related; and (ii) low-dose IGF-I infusion, despite showing significant effects on glucose turnover and lipolysis, does not have preferential metabolic effects compared to insulin, at least when hyperglycemia is present and endogenous insulin secretion is absent.

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