Simultaneous Insulinlike Growth Factor I and Insulin Resistance in Obese Zucker Rats

RALPH J. JACOB, ROBERT S. SHERWIN, KATHLEEN GREENAWALT, AND GERALD I. SHULMAN

It has recently been shown that the ability of insulinlike growth factor I (IGF-I) to stimulate glucose uptake and to lower circulating amino acid levels is retained in insulin-resistant diabetic BB rats. To examine in vivo effects of IGF-I in obese Zucker rats (another model of insulin resistance) 6 obese and 6 lean rats received euglycemic IGF-I infusions (0.65 nmol · kg^{-1} · min^{-1}). IGF-I–stimulated glucose uptake in obese rats was 50% lower than lean control rats (45.0 ± 2.8 vs. 92.2 ± 6.1 μmol · kg^{-1} · min^{-1}, respectively), even though the rise in circulating IGF-I levels was greater in the obese group during IGF-I infusion. In addition, branched chain amino acid concentrations that declined by 45% in lean controls were not suppressed significantly in obese rats (392 ± 33 basal vs. 327 ± 29 μM at 90 min). Equivalent results were observed during euglycemic insulin clamps (12 pmol · kg^{-1} · min^{-1}) in 7 obese and 11 lean rats. These studies demonstrate that obese Zucker rats are resistant to the effects of IGF-I and insulin on glucose and amino acid metabolism. *Diabetes* 41:691–97, 1992

Insulinlike growth factor I (IGF-I) has been shown to lower plasma glucose levels in normal rats and humans (1–3). This effect in the rodent is due primarily to increased peripheral glucose uptake in association with a pronounced stimulation of glycogen synthesis in muscle and liver (1). IGF-I's metabolic effects also extend to protein metabolism. IGF-I is known to augment amino acid transport in vitro (4–6) and inhibit protein breakdown in normal rats (1). Similar IGF-I effects on glucose and protein metabolism have been observed in BB rats with spontaneous autoimmune diabetes (7) and in depancreatized dogs (8). Note that in the diabetic BB rat these metabolic actions of IGF-I are maintained, despite the presence of insulin resistance in this model of insulin-dependent diabetes mellitus (IDDM; 7). In keeping with these results, Rossetti et al. (9) reported that partially depancreatized rats show marked impairment of insulin- but not IGF-I–stimulated rates of cellular glycolysis and glycogen synthesis.

Non-insulin-dependent diabetes mellitus (NIDDM) and obesity are also characterized by hepatic and peripheral insulin resistance (10), although in contrast to insulin-deficient diabetes, these groups display hyperinsulinemia early in the course of disease. Insulin resistance under these conditions appears to be associated with a defect in the glucose transport process (11,12); however, decreased insulin-receptor number and function also have been reported (13–16). Similar defects have been demonstrated for IGF-I's ability to stimulate glucose transport in isolated muscle preparations from NIDDM patients (17) and glucose incorporation into muscle glycogen in obese mice (18); IGF-I receptor structure and function appear normal in these populations (17–19).

This study extends previous observations by examining in vivo whole-body actions of IGF-I in the obese (*fa/fa*) Zucker rat. These animals, which acquire obesity as an autosomal recessive trait (20), maintain normal fasting glucose levels at the expense of hyperinsulinemia (21–23) and display marked glucose intolerance, despite excessive insulin secretion (24). Obese Zucker rats also exhibit marked hepatic and peripheral insulin resistance under conditions of euglycemic hyperinsulinemia (25). To assess whether obese Zucker rats are IGF-I resistant as well, glucose kinetics and circulating amino acids were measured during IGF-I infusion in chronically catheterized awake obese rats under euglycemic conditions.

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Address correspondence and reprint requests to Ralph J. Jacob, Department of Internal Medicine, Fitkin 1, Yale School of Medicine, Box 3333, 333 Cedar Street, New Haven, CT 06015.

Received for publication 11 September 1991 and accepted in revised form 3 March 1992.

RESEARCH DESIGN AND METHODS

Genetically obese Zucker rats (male, 282 ± 6 g, 5–6 wk old) were studied and compared with weight-matched lean (*Fa/?*) Zucker rats (male, 278 ± 8 g, 8–10 wk old). To be more certain of any observed impairment of insulin action, we studied obese animals that were slightly younger than controls; note that they also received more IGF-I per unit of lean tissue (see RESULTS). We also studied a second group of older obese animals (416 ± 12 g, 10–12 wk old) and older lean controls of similar weight (373 ± 12 g, 16–20 wk old). All animals were obtained from Charles River (Wilmington, MA). Catheters were implanted surgically in a carotid artery and jugular vein 1 wk before study, as described previously (1). All animals were fed a diet comprising 19% protein, 10% fat, and 51% carbohydrate (AGWAY Prolab 2000) ad libitum until 24 h before study, when food, but not water, was withdrawn. Catheters were flushed with 0.9% saline on the morning of each experiment and kept patent with a saline infusion (20 μl/min) to which heparin (≤2 U/ml) was added. Subsequent hormone-infusion protocols were conducted with the animals awake and unrestrained.

At the outset, each animal received a primed (9 μCi) plus continuous (0.14 μCi/min) infusion of [3–^{3}H]glucose (Du Pont-NEN, Boston, MA) for 180 min to measure glucose kinetics. After a 90-min tracer equilibration interval, 12 obese rats (7 young and 5 older) and 11 lean rats (7 young and 4 older) received recombinant human IGF-I (Amgen, Thousand Oaks, CA), administered as a 33 nmol/kg bolus followed by a 0.65 nmol · kg^{-1} · min^{-1} continuous infusion. This dose of IGF-I has been used in previous studies (1,7) and would be expected to produce significant hypoglycemia if administered by itself. In additional experiments conducted in 7 obese and 11 lean control animals, insulin was administered (360 pmol/kg prime plus 12 pmol · kg^{-1} · min^{-1} constant i.v.) instead of IGF-I. The insulin dose selected was based on preliminary studies to match the stimulation of whole-body glucose disposal observed during IGF-I infusion in lean Zucker controls (see RESULTS). Fasting plasma glucose levels were maintained throughout using a variable rate dextrose infusion (26).

Plasma samples were obtained at 10-min intervals during the final 30 min of the equilibration and hormone-infusion intervals for measurement of glucose specific activity. Additional aliquots were collected before and at the end of the hormone-infusion period (at 90 min) for analysis of plasma insulin, amino acid, and lactate levels, and for plasma IGF-I in experiments involving IGF-I infusion.

In separate experiments the space of distribution of total-body water was measured in six obese and six lean rats. At t = 0, 100 μCi of ^3H_2O (Du Pont-NEN) was injected intraperitoneally, and tail vein plasma was analyzed for radioactivity at hourly intervals for 1–4 h after injection.

Analytical methods and calculations. Plasma glucose was measured using a Beckman glucose analyzer (Fullerton, CA). Plasma [^{3}H]glucose-specific activity, plasma acidic and neutral amino acids, lactate, and insulin were determined, as described previously (1). Total IGF-I levels were quantitated by radioimmunoassay using acid/ethanol-extracted plasma (Nichols Institute, San Juan Capistrano, CA).

Glucose kinetics were measured during the last 30 min of basal- and hormone-infusion intervals at which time the glucose-specific activity was constant; 1.5 × 10^4 dpm/μmol (coefficient of variation [CV] 4.7%) and 9.2 × 10^3 dpm/μmol (CV 5.1%), respectively. Whole-body glucose uptake and production rates were calculated using steady-state equations (27). Endogenous glucose production rates were calculated during hormone administration by subtracting the amount of infused dextrose from the tracer-derived rate of total glucose appearance during the final 30 min of each protocol. Data expressed as means ± SE were analyzed statistically using analysis of variance followed by post hoc Student's *t* tests to localize effects (CRUNCH Software, San Francisco, CA).

RESULTS

IGF-I and insulin-stimulated glucose metabolism. Rats were matched in terms of body weight (Table 1); as a result, obese animals were ~5 wk younger than lean animals (see METHODS). Although the average weight of obese and lean rats was similar, the space of distribution of water (obtained in a separate group of rats) was 25% less in obese rats compared with lean controls (0.53 ± 0.02 vs. 0.71 ± 0.02 ml/g body wt, obese and lean, respectively, $P < 0.001$). These data were used to estimate glucose flux rates with respect to lean body tissue (μmol/100 ml water) for obese and lean rats.

Obese rats maintained fasting glucose levels that were indistinguishable from lean controls but were hyperinsulinemic (660 ± 105 and 270 ± 45 pM, $P < 0.001$, obese vs. lean from both studies). During the euglycemic insulin clamp study, plasma insulin levels rose 2- to 2.5-fold in both obese and lean animals. In contrast, IGF-I administration produced a 55% decline in plasma insulin, whereas total plasma IGF-I rose to ~120 nM in both groups (Table 1). The increment in plasma IGF-I was, however, significantly greater in obese rats compared with lean controls (114 ± 17 vs. 29 ± 5% above basal in obese and lean rats, respectively, $P < 0.001$).

Lean and obese rats displayed similar rates of glucose flux in the basal state (37.6 ± 1.7 vs. 35.2 ± 1.9 μmol · kg^{-1} · min^{-1}, respectively), despite higher insulin levels in the obese group (Table 1). If turnover rates of glucose are expressed as a function of the volume of metabolically active tissue (per 100 ml of water), however, obese animals show a 23% increase in basal rates of glucose flux compared with lean controls (6.6 ± 0.3 vs. 5.4 ± 0.2 μmol · 100 ml^{-1} water · min^{-1}, respectively, $P < 0.01$).

The dosages of IGF-I and insulin selected produced a comparable 2.5-fold stimulation of glucose uptake in lean Zucker rats (to 92.2 ± 6.1 and 89.4 ± 6.1 μmol · kg^{-1} · min^{-1} or 13.3 ± 1.1 and 12.8 ± 1.1 μmol · 100 ml^{-1} water · min^{-1} during IGF-I and insulin, respectively, NS; Fig. 1). Despite higher circulating insulin levels in obese rats during insulin infusion (vs. lean), total glucose uptake did not rise significantly in

TABLE 1
Hormone levels during euglycemic insulinlike growth factor I and insulin-clamp studies

	Insulinlike growth factor I		Insulin	
	Lean	Obese	Lean	Obese
Body weight (g)	278 ± 8	282 ± 6	283 ± 7	283 ± 11
Plasma				
Glucose (mM)				
Basal	5.9 ± 0.2	6.2 ± 0.3	5.9 ± 0.2	6.4 ± 0.5
Stimulated	5.9 ± 0.2	6.1 ± 0.2	5.8 ± 0.1	6.3 ± 0.4
Insulin (pM)				
Basal	195 ± 15	735 ± 135*	330 ± 75	555 ± 135
Stimulated	105 ± 15†	345 ± 105†	795 ± 120†	1155 ± 255†
Insulinlike growth factor I (nM)				
Basal	94 ± 5	59 ± 6*		
Stimulated	120 ± 5†	121 ± 4†		

Circulating insulinlike growth factor I and insulin levels were collected at t = 0 (basal) and t = 90 (stimulated). Plasma glucose represents the average values during the last 30 min of basal and hormone infusion periods. Values are means ± SE.
*$P < 0.05$ vs. lean controls (analysis of variance).
†$P < 0.05$ vs. basal (analysis of variance).

these animals (36.7 ± 3.3 basal vs. 37.8 ± 2.2 μmol · kg^{-1} · min^{-1} from 60 to 90 min). Similarly, IGF-I administration produced only a 34% increase in glucose uptake over basal levels in obese rats (33.9 ± 2.2 to 45.0 ± 2.8 μmol · kg^{-1} · min^{-1}). The increase in glucose uptake was 15–20% of that caused by IGF-I in lean rats ($P < 0.001$). In keeping with these findings, average rates of infused dextrose required to counteract IGF-I's and insulin's hypoglycemic actions in obese rats were 83 and 97% lower, respectively, than in lean controls ($P < 0.001$; Table 2).

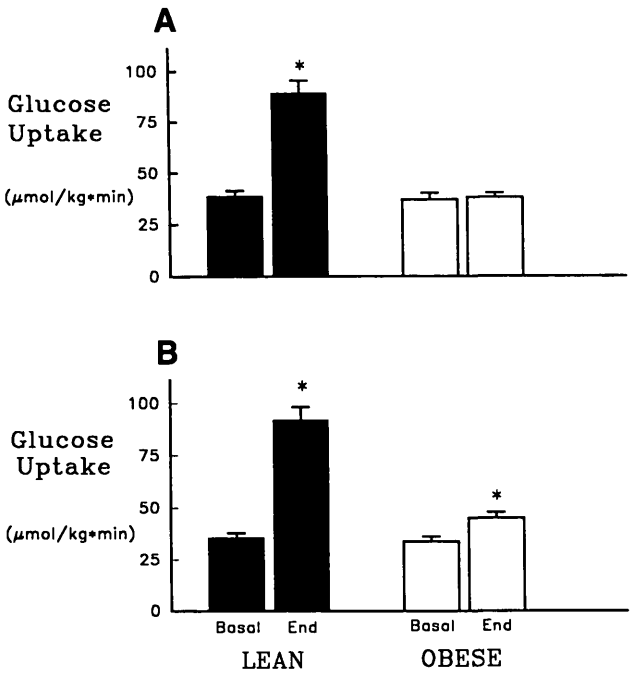

FIG. 1. Insulin- stimulated (*A*) and insulinlike growth factor I–stimulated (*B*) rates of whole-body glucose uptake in lean and obese Zucker rats. Values are means ± SE for samples collected at 10-min intervals over the final 30 min of equilibration (basal) and hormone-infused intervals (end). Statistical analysis using analysis of variance; *$P < 0.05$ vs. basal.

As shown in Table 2, insulin and IGF-I significantly suppressed rates of the liver's glucose production in lean controls (from 38.9 ± 2.8 to 23.3 ± 3.3 μmol · kg^{-1} · min^{-1} for insulin and from 36.1 ± 2.2 to 29.4 ± 2.8 for IGF-I). Although insulin's effect tended to be greater than that of IGF-I, this difference did not achieve statistical significance ($P < 0.07$). In the obese group insulin infusion failed to diminish hepatic glucose production (36.7 ± 3.3 vs. 35.0 ± 3.3 μmol · kg^{-1} · min^{-1}), whereas glucose production tended to rise during IGF-I administration (33.9 ± 2.2 to 38.3 ± 3.3, NS).

Effects of IGF-I on amino acid and lactate metabolism. As shown in Table 3, the basal concentrations of most amino acids were similar in obese and lean rats, except for glycine, which was lower, and citrulline, which was higher, in obese rats. IGF-I infusion produced significant decreases in nearly all amino acids measured in lean controls. The effect of IGF-I in obese animals tended to be less generalized, and in many cases the magnitude of decline was less compared with lean animals. In particular, branched chain amino acids (BCAAs), which fell 45% in lean animals (from 390 ± 26 to 208 ± 16 μM; Fig. 2), did not change significantly in the obese group (392 ± 33 basal to 327 ± 29 μM IGF-I stimulated). Consequently, during the last 30 min of IGF-I infusion, circulating BCAAs were elevated in obese rats ($P < 0.005$ vs. lean controls).

Postabsorptive concentrations of lactate were comparable in both groups, although obese rats tended to have higher lactate levels (NS vs. lean; Fig. 2). In lean rats, IGF-I infusion resulted in a consistent 36% rise in lactate concentrations (from 0.84 ± 0.19 basal to 1.14 ± 0.15 mM at 90 min, $P < 0.005$), whereas in obese animals IGF-I caused plasma lactate to decline by ~36% (from 1.22 ± 0.22 to 0.73 ± 0.09 mM, $P < 0.05$).

Effect of age on basal and IGF-I–mediated glucose metabolism. Figure 3 compares the effects of IGF-I on glucose metabolism in young and old Zucker rats. Young (8–10 wk) and older (16–20 wk) lean rats showed similar

TABLE 2
Glucose kinetics and glucose infusion rates during insulinlike growth factor and insulin euglycemia infusions

	Insulinlike growth factor I		Insulin	
	Lean	Obese	Lean	Obese
Glucose ($\mu M \cdot kg^{-1} \cdot min^{-1}$)				
Uptake				
Basal	36.1 ± 2.2	33.9 ± 2.2	38.9 ± 2.8	36.7 ± 3.3
Stimulated	92.2 ± 6.1*	45.0 ± 2.8*†	89.4 ± 6.1*	37.8 ± 2.2
Production				
Basal	36.1 ± 2.2	33.9 ± 2.2	38.9 ± 2.8	36.7 ± 3.3
Stimulated	29.4 ± 2.8*	38.3 ± 3.3	23.3 ± 3.3*	35.0 ± 3.3
Infusion				
Basal				
Stimulated	60.0 ± 2.8	10.0 ± 1.7†	68.3 ± 3.3	2.22 ± 0.6†

Values are means ± SE over the last 30 min of equilibration (basal) and hormone infusion intervals (stimulated).
*$P < 0.05$ vs. basal; †$P < 0.05$ vs. lean.

fasting glucose levels (5.66 ± 0.22 vs. 5.88 ± 0.22 mM, respectively) and basal glucose flux rates (36.1 ± 2.2 vs. 32.8 ± 3.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$). Likewise, older (10–12 wk) obese rats maintained normal fasting plasma glucose levels and displayed basal glucose flux rates not significantly different than those in young (5–6 wk) obese rats (28.3 ± 1.1 vs. 33.9 ± 2.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$). Fasting plasma insulin concentration was, however, greater in the older obese group (older 1155 ± 225 vs. younger 735 ± 135 pM, $P < 0.052$). On the other hand, IGF-I–stimulated glucose uptake in older rats was reduced in both obese and lean rats (by 35 and 45%, respectively, $P < 0.05$ vs. young groups; Fig. 3). Plasma insulin levels declined during IGF-I to the same extent in both groups of rats (older −50 ± 14 vs. younger −53 ± 8%).

DISCUSSION

These data demonstrate that obese Zucker rats are resistant to IGF-I's in vivo metabolic actions on whole-body glucose uptake and hepatic glucose production. Two previous studies examining glucose transport in isolated muscle preparations from gold-thioglucose–injected mice (11) and morbidly obese humans (17) have suggested that IGF-I–stimulated glucose utilization may be impaired in obesity. This possibility is further supported by data showing that IGF-I injections in obese mice are less effective in promoting glucose incorporation into muscle glycogen (18). Our study extends these findings by examining IGF-I's effects on whole-body glucose flux and hepatic glucose production in the spontaneously obese insulin-resistant Zucker rat. In addition, we showed that the ability of IGF-I to lower plasma levels of several amino acids was also impaired in these animals, particularly so for BCAAs. These findings differ from those obtained in similar studies in insulin-deficient diabetic animals, which also show insulin resistance (7–9). In those experiments, glucose and amino acid

TABLE 3
The effect of insulinlike growth factor I on plasma amino acid concentrations in lean and obese rats

	Lean (μM)		Obese (μM)	
	Basal	Stimulated	Basal	Stimulated
Taur	162 ± 36 (7)	103 ± 11	124 ± 17 (7)	107 ± 11
Thr	221 ± 20 (7)	130 ± 11*	227 ± 15 (7)	171 ± 11*†
Ser	185 ± 18 (7)	133 ± 11*	158 ± 9 (7)	126 ± 8*
Aspg	23 ± 3 (6)	20 ± 3	32 ± 3 (7)	23 ± 4*
Glu	177 ± 57 (7)	78 ± 5*	128 ± 10 (7)	100 ± 7*
Gln	388 ± 30 (7)	267 ± 10*	362 ± 30 (7)	288 ± 29*
Gly	282 ± 28 (7)	199 ± 6*	193 ± 12 (7)‡	173 ± 7
Ala	225 ± 30 (6)	171 ± 12*	187 ± 16 (7)	118 ± 11*†
Cit	46 ± 6 (6)	30 ± 5*	83 ± 11 (7)‡	66 ± 7*
Val	163 ± 18 (7)	91 ± 13*	173 ± 10 (6)	159 ± 19†
Met	19 ± 4 (5)	9 ± 2	23 ± 4 (6)	16 ± 4*
Ile	84 ± 5 (7)	41 ± 4*	80 ± 6 (7)	67 ± 5†
Leu	144 ± 12 (7)	77 ± 5*	139 ± 14 (7)	115 ± 9†
Tyr	55 ± 3 (7)	31 ± 1*	57 ± 5 (7)	38 ± 4*†
Phe	74 ± 4(7)	51 ± 2*	67 ± 4 (7)	62 ± 3†

Values are mean ± SE (n) for samples collected at t = 0 (basal) and t = 90 min (stimulated).
*$P < 0.05$ vs. basal; †$P < 0.05$, change from basal vs. lean; ‡$P < 0.05$ vs. lean basal.

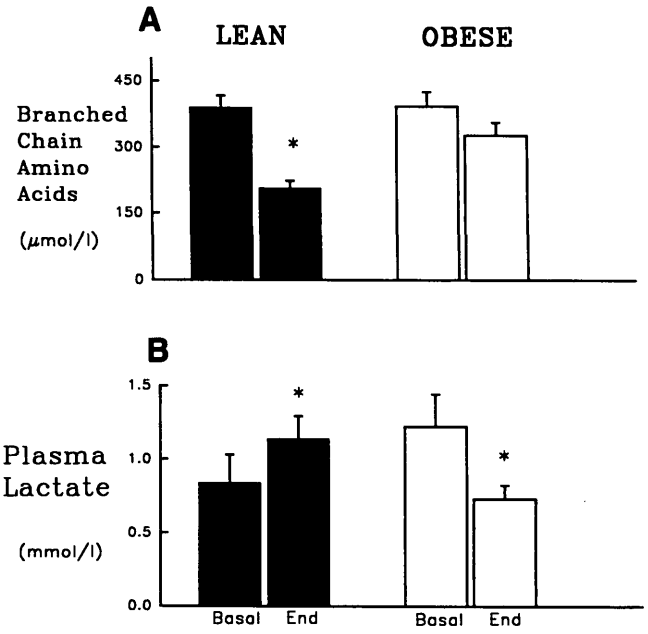

FIG. 2. Circulating branched chain amino acid (*A*) and lactate (*B*) levels during insulinlike growth factor I infusion in lean and obese rats. Values are means ± SE collected at 0 and 90 min during euglycemic studies. *$P < 0.05$ vs. basal.

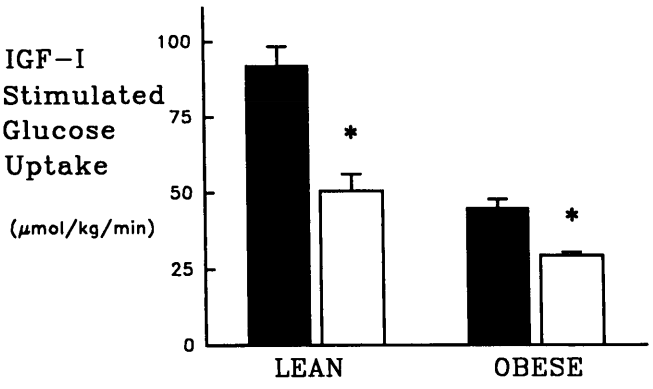

FIG. 3. The effect of age on insulinlike growth factor I–stimulated rates of whole-body glucose uptake in lean and obese Zucker rats. Values are means ± SE levels measured during the final 30 min of insulinlike growth factor I administration. Results using analysis of variance. *$P < 0.05$ vs. young rats. *Solid bars*, young rats; *open bars*, old rats.

responses to IGF-I were indistinguishable from responses observed in control animals.

Previous studies have suggested that IGF-I exerts its effects on glucose and protein metabolism through its own high-affinity receptor in rat (6,11,29) and human muscle tissues (17,19,30). Although IGF-I receptors have not been examined in muscle tissue from Zucker rats, others have failed to demonstrate alterations in IGF-I receptors or their function in obese mice or obese humans (11,18,19), although these groups exhibit a marked impairment of IGF-I's ability to stimulate muscle glucose transport and glycogen synthase activity in vitro (11,17,18). To the extent these observations apply to the Zucker rat, our data showing severe resistance to IGF-I administered in vivo support the idea that a defect(s) in events beyond the receptor account for the defective response to IGF-I in this model.

Similarly, studies of muscle tissue obtained from obese Zucker rats have concluded that the relatively small abnormality in insulin binding observed was not sufficient to explain the degree of insulin resistance in these animals, implying a primary role for abnormal insulin-mediated glucose transport in the obese animal (13). Recent work that examined abnormal glucose transport processes in tissues from insulin-resistant animals and humans provide further evidence implicating altered transporter processing. In preliminary reports, Wallberg-Henriksson et al. (31) and Matthaei et al. (32) demonstrated that normalization of glucose transport in muscle tissue from NIDDM patients and isolated adipocytes from obese Zucker rats was sufficient to restore in vivo sensitivity to insulin. It is not known whether in vivo response to IGF-I could be restored with similar treatment. However, inasmuch as the metabolic effects of these two hormones are mediated through different receptors and based on reports that concluded the stimulatory actions of IGF-I and insulin on glucose transport are mediated primarily through the same transport system (29,33), these data suggest common postreceptor defect(s) may underlie the impaired responses to both hormones.

It is also possible that altered fat metabolism in the obese Zucker rat contributed to the resistance observed in response to IGF-I and insulin infusions. Obese rats are known to have both increased numbers of fat cells and larger individual adipocytes (34–36). Exaggerated rates of lipolysis brought about by these changes could inhibit glucose utilization via the glucose-fatty acid cycle (37). It is not known to what extent this abnormal lipid metabolism contributes to defects in insulin- and IGF-I–mediated glucose metabolism observed in the obese Zucker rat. Note that glucose uptake by fat tissue contributes significantly to basal whole-body glucose turnover in obese (but not lean) rats. In this regard, Bolinder et al. (38) reported that IGF-I–mediated transport of glucose into isolated fat cells from NIDDM patients was blunted, although this finding was not confirmed by a subsequent study (39). Therefore, it is possible that decreased uptake of whole-body glucose reflects not only a peripheral lean tissue defect but may involve abnormal IGF-I–mediated glucose uptake and metabolism in adipocytes as well.

Our findings agree with previous data showing that obese Zucker rats are resistant to insulin's inhibitory effect on hepatic glucose production (22,24,25). These whole-body data are consistent with defects in insulin binding and insulin-mediated postbinding events observed in liver and muscle tissue of obese Zucker rats (13,16) and humans (14,28). Interestingly, our data suggest that lean Zucker rats also display impaired hepatic sensitivity to insulin. Although insulin infusion did suppress hepatic glucose production (38%) in lean Zucker controls, this decline was clearly less than the 65-85% reduction in glucose production we previously reported in Sprague-Dawley and diabetes-resistant BB rats during insulin administration ($P < 0.05$ and $P < 0.001$, respectively; 1,7). The relative impairment in the liver's response to insulin in lean Zucker rats occurred, despite basal and infused levels of plasma insulin that were higher in lean Zucker rats ($P < 0.005$).

This study also demonstrates an alteration of IGF-I–stimulated amino acid metabolism in obese rats. Postabsorptive levels of most circulating amino acid levels in the obese group were comparable with those in lean controls, although markedly lower glycine values were observed in this and other studies (40,41). However, the amino acid response to IGF-I, particularly that of BCAAs, was significantly reduced in obese Zucker rats. In contrast, the amino acid lowering effect of IGF-I was not altered in another example of insulin resistance, the insulin-dependent BB rat (7). We previously reported that IGF-I's ability to lower circulating BCAA levels is due to a suppression of protein breakdown. The failure of IGF-I to significantly lower BCAA in obese Zucker rats is consistent with the possibility that these animals also have a defect in IGF-Is antiproteolytic effect.

Interestingly, the effects of IGF-I on glucose metabolism are attenuated in older Zucker rats, not unlike the insulin resistance that occurs during the aging process in humans (42). Although these studies were not precisely age matched to animals included in previous studies (1,7), the older lean Zucker rats were similar in age to Sprague-Dawley and normal BB rats that received IGF-I

in earlier reports. Note that IGF-I–stimulated glucose uptake in Zucker rats was only 50% above basal compared with 100-150% in those other strains. Thus, even lean Zucker rats may have an underlying predisposition to IGF-I resistance.

In summary, our data demonstrate that obese Zucker rats are IGF-I and insulin resistant, although the actions of these hormones on glucose and amino acid metabolism appear to be mediated through different receptors. These findings suggest a common postreceptor defect may underlie impaired in vivo responses to both hormones.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (DK-40936) and the Juvenile Diabetes Foundation.

We thank James A. Miller (Amgen Biologicals) for graciously supplying us with human recombinant IGF-I. We also are indebted to Aida Grozmann and Andrea Belous for measurements of plasma insulin and total IGF-I.

REFERENCES

1. Jacob R, Barrett E, Plewe G, Fagin K, Sherwin RS: Acute effects of insulin-like growth factor I on glucose and amino acid metabolism in the awake fasted rat: comparison with insulin. *J Clin Invest* 83:1717–23, 1989
2. Zapf J, Hauri C, Waldvogel M, Froesch ER: Acute metabolic effects and half-lives of intravenously administered insulin-like growth factors I and II in normal and hypophysectomized rats. *J Clin Invest* 77:1768–75, 1986
3. Guler HP, Zapf J, Froesch ER: Short-term metabolic effects of recombinant human insulin-like growth factor I in healthy adults. *N Engl J Med* 317:137–40, 1987
4. Hill DJ, Crace CJ, Strain AJ, Milner RDG: Regulation of amino acid uptake and deoxyribonucleic acid synthesis in isolated human fetal fibroblasts and myoblasts: effect of human placental lactogen, somatomedin-C, multiplication-stimulating activity, and insulin. *J Clin Endocrinol & Metab* 62:753–60, 1986
5. Sasaoka T, Kobayashi M, Takata Y, Ishibashi O, Iwasaki M, Shigeta Y, Goji K, Hisatomi A: Clarification of signaling pathways mediated by insulin and insulin-like growth factor I receptors in fibroblasts from patients with specific defect in insulin receptor. *Diabetes* 37:1515–23, 1988
6. Yu K, Czech MP: The type I insulin-like growth factor receptor mediates the rapid effects of multiplication-stimulating activity on membrane transport systems in rat soleus muscle. *J Biol Chem* 259:3090–95, 1984
7. Jacob RJ, Sherwin RS, Bowen L, Fryburg D, Fagin KD, Tamborlane WV, Shulman GI: Metabolic effects of IGF-I and insulin in the spontaneously diabetic BB/w rat. *Am J Physiol* 260:E262–68, 1991
8. Giacca A, Gupta R, Efendic S, Hall K, Skottner A, Lickley L, Vranic M: Differential effects of IGF-I and insulin on glucoregulation and fat metabolism in depancreatized dogs. *Diabetes* 39:340–47, 1990
9. Rossetti L, Frontoni S, Dimarchi R, DeFronzo RA, Giaccari A: Metabolic effects of IGF-I in diabetic rats. *Diabetes* 40:444–48, 1991
10. DeFronzo RA, Simonson D, Ferrannini E: Hepatic and peripheral insulin resistance: a common feature in non-insulin dependent and insulin dependent diabetes. *Diabetologia* 23:313—19, 1982
11. Poggi C, Le Marchand-Brustel Y, Zapf J, Froesch ER, Freychet P: Effects of binding of insulin-like growth factor I in the isolated soleus muscle of lean and obese mice: comparison with insulin. *Endocrinology* 105:723–30, 1979
12. Garvey WT, Huecksteadt TP, Matthaei S, Olefsky JM: Role of glucose transporters in the cellular insulin resistance of type II non-insulin-dependent diabetes mellitus. *J Clin Invest* 81:1528–36, 1988
13. Crettaz M, Prentki M, Zaninetti D, Jeanrenaud B: Insulin resistance in soleus muscle from obese Zucker rats. *Biochem J* 186:525–34, 1980
14. Caro JF, Sinha MK, Raju SM, Ittoop O, Pories WJ, Flickinger EG, Meelheim D, Dohm GL: Insulin receptor kinase in human skeletal muscle from obese subjects with and without noninsulin dependent diabetes. *J Clin Invest* 79:1330–37, 1987
15. Kolterman OG, Gray RS, Griffin J, Bernstein P, Insel J, Scarlett JA, Olefsky JM: Receptor and post receptor defects contribute to the insulin resistance in non-insulin-dependent diabetes mellitus. *J Clin Invest* 68:957–69, 1981
16. Mahmood HA, Wood PJ, Marks V: The effect of induced hyperglucagonaemia on the Zucker fatty rat. *Diabetologia* 14:405–12, 1978
17. Dohm GL, Elton CW, Raju MS, Mooney ND, DiMarchi R, Pories WJ, Flickinger EG, Atkinson SM Jr, Caro JF: IGF-I–stimulated glucose transport in human skeletal muscle and IGF-I resistance in obesity and NIDDM. *Diabetes* 39:1028–32, 1990
18. Cascieri MA, Slater EE, Vicario PP, Green BG, Bayne ML, Saperstein R: Impaired insulin-like growth factor I-mediated stimulation of glucose incorporation into glycogen in vivo in the *ob/ob* mouse. *Diabetologia* 32:342–47, 1989
19. Livingston JN, Pollare T, Kithell H, Arner P: Characterization of insulin-like growth factor I receptor in skeletal muscles of normal and insulin resistant subjects. *Diabetologia* 31:871–77, 1988
20. Zucker LM, Zucker TF: Fatty, a new mutation in the rat. *J Hered* 52:275–78, 1961
21. Stern JS, Johnson PR, Greenwood MRC, Zucker LM, Hirsch J: Insulin resistance and pancreatic insulin release in the genetically obese Zucker rat. *Proc Soc Exp Biol Med* 139:66–69, 1972
22. Zucker LM, Antoniades . Insulin and obesity in the Zucker genetically obese rat "fatty." *Endocrinology* 90:1320–30, 1972
23. Stern JS, Johnson PR, Batchelor BR, Zucker LM, Hirsch J: Pancreatic insulin release and peripheral tissue resistance in Zucker obese rats fed high- and low-carbohydrate diets. *Am J Physiol* 228:543–48, 1975
24. Ionescu E, Sauter JF, Jeanrenaud B: Abnormal oral glucose tolerance in genetically obese (fa/fa) rats. *Am J Physiol* 248:E500–506, 1985
25. Terrettaz J, Jeanrenaud B: In vivo hepatic and peripheral insulin resistance in genetically obese (fa/fa) rats. *Endocrinology* 112: 1346–51, 1983
26. Smith D, Rossetti L, Ferrannini E, Johnson CM, Cobelli C, Toffalo G, Katz LD, DeFronzo RA: In vivo glucose metabolism in the awake rat: tracer and insulin clamp studies. *Metab Clin Exp* 36:1167–74, 1987
27. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA: Correction of hyperglycemia with Phlorizin normalizes tissue sensitivity to insulin in diabetic rats. *J Clin Invest* 79:1510–15, 1987
28. Caro JF, Ittoop O, Pories Wj, Meelheim D, Flickinger EG, Thomas F, Jenquin M, Silverman JF, Khazanie PG, Sinha MK: Studies on the mechanism of insulin resistance in the liver from humans with noninsulin-dependent diabetes. *J Clin Invest* 78:249–58, 1986
29. Meuli C, Froesch ER: Insulin and nonsuppressible insulin–like activity (NSILA-S) stimulate the same glucose transport system via two separate receptors in rat heart. *Biochem Biophys Res Commun* 75:689–95, 1977
30. Zorzano A, James DE, Ruderman NB, Pilch PF: Insulin-like growth factor I binding and receptor kinase in red and white muscle. *FEBS Lett* 234:257–62, 1988
31. Wallberg-Henriksson H, Galuska D, Thorne A, Sonnenfeld: Metformin increases insulin-stimulated glucose transport in insulin-resistant human skeletal muscle (Abstract). In *Glucophage Symposium Helsingor, 1990*, p. 43
32. Matthaei S, Reibold JP, Klein HH, Benecke H, Hamann A, Greten H: Effect of in vivo Metformin-treatment on insulin binding, glucose transport, activation of insulin receptor kinase in intact cells, and subcellular distribution of GLUT-1 and GLUT-4 glucose transporters in adipocytes from obese (*fa/fa*) Zucker rats (Abstract). *In Proc Annu Meet Endocrinol Soc, 72nd, Atlanta, GA, 1990*, p. 46
33. Sowell MO, Robinson KA, Buse MG: Phenylarsine oxide and denervation effects on hormone-stimulated glucose transport. *Am J Physiol* 255:E159–65, 1988
34. Bray GA: Studies on the composition of adipose tissue from the genetically obese rats. *Proc Soc Exp Biol Med* 131:1111–14, 1969
35. Johnson PR, Zucker LM, Cruce JAF, Hirsch J: Cellularity of adipose depots in the genetically obese Zucker rat. *J Lipid Res* 12:706–14, 1971
36. Stern JS, Greenwood MRC: A review of development of adipose cellularity in man and animals. *Fed Proc* 33:1952–55, 1974
37. Randle PJ, Garland PB, Newsholme EH, Hales CM: The glucose fatty acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1:785–89, 1963
38. Bolinder J, Lindblad A, Engfeldt P, Arner P: Studies of acute effects of insulin-like growth factors I and II in human fat cells. *J Clin Endocrinol Metab* 65:732–37, 1987
39. Sinha MK, Buchanan C, Reneri C, Khazanie P, Pories WJ, DiMarchi R, Caro JF: IGF-I–stimulated glucose transport, IGF-I receptors and

tyrosine kinase are not altered as noted for insulin in adipocytes from NIDDM patients (Abstract). *Diabetes* 38 (Suppl. 1):103A, 1989
40. Finkelstein JA, Chance WT, Fischer JE: Brain serotonergic activity and plasma amino acid levels in genetically obese Zucker rats. *Pharmacol Biochem Behav* 17:939–44, 1982
41. Tsuda TT, Ohkubo T, Kamiguchi H, Tsuda M, Katsunuma T, Yamamura M: Influence of fecal anorexigenic substance (FS-T) on plasma amino acids in Wistar and Zucker obese (fa/fa) rats. *J Nutr* 119:1327–32, 1989
42. DeFronzo RA: Glucose intolerance and aging: evidence for tissue insensitivity to insulin. *Diabetes* 28:1095–1101, 1979