**Insulin Sensitivity of Suppression of Endogenous Glucose Production Is the Single Most Important Determinant of Glucose Tolerance**

Peter N. Båvenholm, Jan Pigon, Claes-Göran Östenson, and Suad Efendic

Hyperglycemia results from an imbalance between endocrine pancreatic function and hepatic and extrahepatic insulin sensitivity. We studied 57 well-matched Swedish men with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or mild diabetes. Oral glucose tolerance and insulin release were assessed during an oral glucose tolerance test (OGTT). Insulin sensitivity and glucose turnover were determined during a two-step euglycemic insulin clamp (infusion 0.25 and 1.0 mU·kg⁻¹·min⁻¹). High-performance liquid chromatography–purified [6-³H]glucose was used as a tracer. During low-insulin infusion, the rate of endogenous glucose production (EGP) decreased more in subjects with NGT than in subjects with IGT or diabetes (β rate of appearance [Rₐ] 1.25 ± 0.10 vs. 0.75 ± 0.14 vs. 0.58 ± 0.09 mg·kg⁻¹·min⁻¹, P < 0.001). The corresponding rates of glucose infusion during the high-dose insulin infusion (M values) were 8.3 ± 0.6 vs. 5.4 ± 0.9 vs. 4.7 ± 0.4 mg·kg⁻¹·min⁻¹ (P < 0.001). A total of 56% of the variation in glucose area under the curve (AUC) during OGTT (glucose AUC) was mainly explained by β Rₐ (increase in multiple R² 0.42) but also by β Rₐ (rate of disappearance) (increase in multiple R² 0.05), and the early insulin response during OGTT contributed significantly (increase in multiple R² 0.07). When M value was included in the model, reflecting extrahepatic insulin sensitivity, it contributed to 20% of the variation in glucose AUC, and together with the incremental insulin response (increase in multiple R² 0.21), it explained 45% of the variation. In conclusion, insulin sensitivity of suppression of EGP plays the most important role in the determination of blood glucose response during OGTT. *Diabetes* 50:1449–1454, 2001

Normal glucose tolerance (NGT) is mainly a function of the interplay between insulin sensitivity (muscle, liver, and adipocytes) and endocrine pancreatic function (1–3). This is evident from studies showing that insulin resistance (comparable with what is found in type 2 diabetes) with ensuing hyperinsulinemia is prevalent in ~25% of individuals with NGT (4), whereas subjects that are characterized by a low insulin response maintain NGT by exhibiting increased extrahepatic insulin sensitivity (5). The pathogenesis of glucose intolerance is often complex and includes both decreased insulin release and decreased insulin sensitivity. Accordingly, it has long been debated whether impaired insulin secretion or decreased insulin sensitivity in liver and/or extrahepatic tissues or a combination thereof is the primary defect. The results from several longitudinal studies that aimed to evaluate these components are contradictory and limited by the fact that insulin release and peripheral insulin sensitivity were often not assessed simultaneously (6–10).

Whereas there is ample evidence that fasting blood glucose levels are mainly determined by the rate of endogenous glucose production (EGP) (2,11), which mechanisms regulate variability in postprandial glycemia is less clear. Thus, the relative changes in the rates of glucose appearance and disappearance after a mixed meal or an oral glucose load are determined by islet β- and α-cell responsiveness, hepatic and extrahepatic insulin sensitivity, glucose effectiveness, etc. (12–14). The aim of the present study was to evaluate the impact of insulin sensitivity on suppression of EGP versus insulin sensitivity in muscle versus insulin release to the variation in OGTT. For that purpose, we studied 57 well-matched middle-aged Swedish men with either normal, impaired, or decreased OGTT. EGP and glucose uptake were determined during a two-step hyperinsulinemic-euglycemic clamp with a matched-step tracer infusion (MSTI) technique (15,16). In this study, under these experimental conditions, the hepatic glucose production accounted for ~95% of the rate of EGP (17). Insulin response was evaluated during OGTT.

**RESEARCH DESIGN AND METHODS**

A total of 57 Swedish men who had NGT (n = 31), impaired glucose tolerance (IGT) (n = 12), or mild diabetes (n = 14) were recruited and invited to participate in the study. The control subjects belonged to a larger population-based group of middle-aged men and, together with the patients, were the first consecutive subjects to fulfill the inclusion criteria. All three groups were...
matched for sex, age, and BMI. Subjects with a BMI 22–34.5 kg/m² were considered eligible. None of these subjects had signs of chronic disease (except diabetes) or were on lipid-lowering drugs. All subjects were given both written and oral information concerning the nature and potential risks of the study, and each subject gave informed consent. The experimental protocol was approved by the Ethics Committee at Karolinska Hospital.

Metabolic investigations were performed after 12 h of fasting and started at 8 a.m. All subjects were free of symptoms of infectious disease at the time of investigations. The participants were asked to maintain their normal physical activity and diet for at least 3 days before the investigations. The first day after a weekend was never used for investigations. All clinical and metabolic tests were performed with participants in a 4- to 6-week period and were evenly distributed throughout the year.

OGTT. Oral glucose tolerance and the incremental insulin response (0–30 and 0–120 min) were assessed during OGTT (18). A total of 75 g of glucose was dissolved in 250 ml of water. The area under the curve (AUC) was calculated for glucose during OGTT. Insulin response was calculated as the incremental insulin area (above fasting insulin concentration) between 0 and 30 and between 0 and 120 min during the OGTT. Insulinogenic index was calculated as the incremental insulin area/glucose AUC between 0 and 120 min.

Hyperinsulinemic-euglycemic clamp. Sequential two-step hyperinsulinemic-euglycemic clamps were performed after a 150-min basal and tracer equilibration period. At the onset of the experiment, a bascilic vein of each arm was cannulated, one for sampling and the other for infusion. Both arms were put into a heated (50°C) sleeve. A third catheter was introduced into the cephalic vein of the arm used for infusions, for continuous sampling of arterial and venous blood. Glucose was measured by a Biostator (Glucose Controlled Insulin Infusion System; Miles Laboratories, Life Science Instruments, Elkart, IN). A primed continuous infusion of [6-3H]glucose was administered throughout the study with a syringe pump (IMED; Medical Market) (see “Tracer methods”). Basal sampling for plasma specific activity was performed during the last 30 min of the basal period. Afterward, two levels of hyperinsulinaemia of 150-min duration each were induced by intravenous infusion of 0.25 and 1.0 μM·kg⁻¹·min⁻¹ human rapid-acting insulin (NovoRapid; Novo Nordisk, Bagsvaerd, Denmark) (0.2 IU/ml with 4 mg/ml of human albumin in saline). Euglycemia was maintained by using a Biostator, which calculated glucose infusion rate from the reading of blood glucose measurements during the previous 4 min, according to an algorithm (19). Potassium (0.15 mmol/l glucose) was added to the infusate.

Calculations of body composition and physical fitness. Lean body mass (LBM) was calculated using DEXA (LUNAR DPX-L, X-Ray Bone Densitometer, version 1.3Z, Lunar). Physical fitness was determined as the maximal working capacity (V0₂max) performed on an electrically braked cycloergometer. After a short period of exercise at 30 W, the load was increased in a stepwise manner by 30 W every minute, until exhaustion or dyspnoea. A 12-lead electrocardiograph was recorded during the test.Expired gases were sampled through a non–steady state equation of Steele as modified by DeBodo with a pool fraction of 0.65 and an extracellular volume of 250 ml/kg (26). During clamp experiments, the rate of hepatic glucose production was calculated by subtracting the glucose infusion rate from the rate of glucose appearance measured by the tracer. Data were smoothed with the optimal-segments technique using the optimal error algorithm (27).

Statistical analysis. All values are presented as means ± SE. Logarithmic transformation was performed on all skewed variables to obtain a normal distribution before statistical computations and significance testing were undertaken. When two sets of data were compared, a Student’s paired t test was used to evaluate statistical differences. Differences in continuous variables between groups were tested by analysis of variance (ANOVA) with the Scheffe test used as a post hoc test or by analysis of covariance using BMI and V0₂max as covariables. Multiple stepwise linear regression analysis was used to study the independent influence of insulin response and hepatic and extrahepatic insulin sensitivity on the variation of glycemic response during OGTT. The models have been checked by inspection of residuals. Partial correlation coefficients were calculated using age as a forced variable in the equations.

RESULTS

Basic characteristics of the study population. The subjects were divided into three groups based on OGTT and matched for age (mean age of study group 47.0 ± 5.7), LBM, and physical fitness (Table 1). Subjects with IGT tended to have a higher BMI and a lower V0₂max, although these differences were not statistically significant. Two-hour plasma glucose concentrations during OGTT were 5.3 ± 0.2, 7.9 ± 0.3, and 12.2 ± 0.7 in subjects with NGT, IGT, and diabetes (ANOVA, P < 0.001), respectively. The early insulin response during OGTT (0–30 min) tended to be lower in subjects with diabetes compared with the subjects with NGT and IGT (P = 0.08, ANOVA), whereas total incremental insulin response during OGTT was significantly lower in subjects with diabetes compared with subjects with IGT (P < 0.01) (Table 1). The insulinogenic index (incremental insulin/glucose AUC) >0–120 min was diminished in the diabetic subjects (P < 0.001, ANOVA), indicating an inappropriate insulin response (Table 1). Fasting plasma insulin concentration was elevated in patients with mild diabetes (P < 0.05 vs. NGT) and tended to be increased in subjects with IGT compared with those with NGT, although statistical significance was not reached. Using BMI and V0₂max as covariates did not change the statistical results obtained with ANOVA (Table 1).

Two-step euglycemic-hyperinsulinemic clamp. To maintain normoglycemia (plasma glucose 5.1 mmol/l) during high insulin-infusion rates, it was necessary to infuse glucose at rates of 8.3 ± 0.6 mg·kg⁻¹·min⁻¹ (M value) in subjects with NGT (Table 1). The corresponding M values were significantly lower in subjects with IGT (5.4 ± 0.9 mg·kg⁻¹·min⁻¹, P < 0.05) and patients with diabetes (4.7 ± 1.4 mg·kg⁻¹·min⁻¹, P < 0.001 vs. NGT). Similarly, the difference in R₂ during high-dose insulin infusion rate and equilibrium was lower in both IGT subjects (3.3 ± 0.8 mg·kg⁻¹·min⁻¹, P < 0.05 vs. NGT) and diabetic subjects (2.7 ± 0.3 mg·kg⁻¹·min⁻¹, P < 0.001 vs. NGT) compared with NGT subjects (6.2 ± 0.6 mg·kg⁻¹·min⁻¹) (data not shown). Fasting free fatty acid (FFA) concentrations and FFA levels during low- and high-dose infusion rates were significantly higher in subjects with IGT and patients

supernatant was passed through anion and cation exchange columns (AG 2·X8 and AG 50W·X8, Bio-Rad Laboratories, Richmond, CA) to remove labeled metabolites of glucose, lyophilized to remove tritiated water, reconstituted with 7 ml of water, and counted in a β-scintillation counter. Samples of both tracer infusate and glucose infused were measured in the same way after appropriate dilution. Glucose appearance (R₂) was calculated using the non–steady state equation of Steele as modified by DeBodo with a pool fraction of 0.65 and an extracellular volume of 250 ml/kg (26). During clamp experiments, the rate of hepatic glucose production was calculated by subtracting the glucose infusion rate from the rate of glucose appearance measured by the tracer. Data were smoothed with the optimal-segments technique using the optimal error algorithm (27).
with diabetes than in subjects with NGT (Table 1), whereas glucagon concentrations did not vary among the three groups (data not shown). There was no variation in basal EGP among the groups, whereas EGP was suppressed by 63% in subjects with NGT, by 43% in those with IGT, and by 31% in diabetic patients after low-dose insulin infusion (0.25 mU kg\(^{-2}\) min\(^{-1}\)) (Fig. 1).

Multiple stepwise regression analysis was applied to evaluate the independent contributions of insulin response, insulin sensitivity of suppression of EGP, and extrahepatic insulin sensitivity to the variation in oral glucose tolerance (Table 2). Age was used as a forced variable in all equations. A total of 56% of the variation in glycemic response during OGTT was mainly explained by the magnitude of the decrease in \(R_a\) during the low-insulin infusion rate (increase in multiple \(R^2\) 0.41), to a lesser extent by the increase in \(R_d\) (increase in multiple \(R^2\) 0.06), and by the early insulin response during OGTT (increase in multiple \(R^2\) 0.19).

When the \(M\) value was included in the model (Table 3), it contributed to 20% of the variation in glycemic responses during OGTT, and together with the incremental insulin response during OGTT (increase in multiple \(R^2\) 0.19), it explained 45% of the variation. Controlling for BMI, LBM, or \(V_{O2max}\) did not significantly alter the outcome of any of the models (data not shown).

### TABLE 1
Characteristics of the study group (n = 57)

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
<th>Type 2 diabetes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>12</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.3 ± 1.1</td>
<td>44.0 ± 1.6</td>
<td>48.9 ± 0.9</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.3 ± 0.4</td>
<td>28.0 ± 1.2</td>
<td>26.7 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td>% Lean body weight</td>
<td>69.2 ± 1.0</td>
<td>67.5 ± 1.5</td>
<td>66.9 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>(V_{O2max}) (O(_2) kg(^{-1}) min(^{-1}))</td>
<td>31.2 ± 1.3</td>
<td>26.6 ± 1.4</td>
<td>28.8 ± 1.1</td>
<td>0.14</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose (mmol/l)</th>
<th>Fasting glucose</th>
<th>Glucose AUC (0–120 min)</th>
<th>Fasting insulin (pmol/l)</th>
<th>Insulin 0–30 min</th>
<th>Insulin 0–120 min</th>
<th>Insulin/glucose AUC 0–120 min</th>
<th>M value (mg kg(^{-1}) min(^{-1}))</th>
<th>FFA (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.5 ± 0.1</td>
<td>776 ± 22</td>
<td>120 ± 8</td>
<td>1,708 ± 164</td>
<td>8,475 ± 811</td>
<td>11 ± 1.1</td>
<td>8.3 ± 0.6</td>
<td>0.45 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>5.0 ± 0.2(^)</td>
<td>1,033 ± 55(^)</td>
<td>155 ± 20</td>
<td>2,007 ± 369</td>
<td>13,411 ± 2,533</td>
<td>14 ± 2.9</td>
<td>5.4 ± 0.9(^)</td>
<td>0.66 ± 0.07 (^)</td>
</tr>
<tr>
<td></td>
<td>6.7 ± 0.3(^)</td>
<td>1,385 ± 55(^)</td>
<td>173 ± 16(^)</td>
<td>1,217 ± 120</td>
<td>6,589 ± 865(^)</td>
<td>5.0 ± 0.7(^)</td>
<td>4.7 ± 0.4(^)</td>
<td>0.53 ± 0.04</td>
</tr>
</tbody>
</table>

Data are means ± SEM. *P < 0.001 compared with NGT; †P < 0.01 compared with NGT; ‡P < 0.05 compared with NGT; §P < 0.01 compared with IGT; ¶P < 0.001 compared with IGT. ANOVA (differences between patient groups and control subjects). The Scheffe F test was used to identify differences between the groups when the overall F statistics were significant.

FIG. 1. The hepatic glucose production rate (\(R_a\)) during postabsorptive conditions and the low-dose insulin infusion rate (0.25 mU kg\(^{-1}\) min\(^{-1}\)) in subjects with NGT (n = 31), IGT (n = 12), and in subjects with type 2 diabetes (n = 14).
TABLE 2
Multiple stepwise regression analysis in all subjects with or without mild type 2 diabetes using glucose AUC during an OGTT as a dependent variable

<table>
<thead>
<tr>
<th>Glucose AUC</th>
<th>Partial correlation coefficient</th>
<th>Final model* increase in multiple $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.184</td>
<td>0.034</td>
</tr>
<tr>
<td>OGTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin 0–30 min</td>
<td>$-0.282^\dagger$</td>
<td>0.068</td>
</tr>
<tr>
<td>Insulin 0–120 min</td>
<td>$-0.225$</td>
<td></td>
</tr>
<tr>
<td>$R_1$ (mg · kg$^{-1}$ · min$^{-1}$)</td>
<td>$-0.446^\dagger$</td>
<td>0.046</td>
</tr>
<tr>
<td>$\Delta R_2$ (mg · kg$^{-1}$ · min$^{-1}$)</td>
<td>$-0.656^\dagger$</td>
<td>0.416</td>
</tr>
<tr>
<td>Multiple $R^2$</td>
<td></td>
<td>0.564</td>
</tr>
</tbody>
</table>

Data are correlation coefficients when age had first been entered in the regression model. *Variables included in the multiple regression analysis and their respective contribution to the value of multiple $R^2$; $^\dagger P < 0.001$.

DISCUSSION
The present study was undertaken to examine the relative contributions of insulin responsiveness and both insulin sensitivity of suppression of EGP and extrahepatic insulin sensitivity to the variations in oral glucose tolerance. For this purpose, we studied three well-matched groups of mildly overweight middle-aged men who had normal, impaired, or decreased OGTT and used a multiple stepwise regression analysis approach for calculating the independent contributions of the parameters studied to the variation in oral glucose tolerance. Our data suggest that the low-insulin infusion-mediated suppression of EGP was the single most important determinant of oral glucose tolerance in this group of subjects. In addition, extrahepatic insulin sensitivity and insulin response during OGTT independently contributed to the variation in oral glucose tolerance.

In the present study, we evaluated insulin responsiveness during OGTTs, whereas insulin sensitivity of suppression of EGP and extrahepatic insulin sensitivity were determined using established and validated methods for determination of glucose turnover (15,16). Because in this study hepatic glucose production accounts for >95% of EGP (17), the present findings suggest that a hyperglycemic response to OGTT largely depends on insulin-mediated mechanisms and that hepatic insulin resistance is an early and important defect characterizing subjects with IGT and mild diabetes. Meyer and colleagues (28,29) reported that kidneys contribute as much as 15% to EGP in overnight-fasting subjects. The differences in the reported renal contributions to glucose production may reflect difficulties in measuring small-concentration differences in the fractional extraction of $^3$H-glucose, particularly when the measurement is performed across kidney, because of a relatively high blood flow.

Also in the present study, the use of HPLC-purified tracer with the MSTI technique maintained plasma specific activity within 20% of the basal value throughout the clamp, well within acceptable limits (15,16). Moreover, no group differences in plasma specific activity were observed. EGP was fully suppressed during the high–insulin dose infusion, allowing for determination of extrahepatic insulin sensitivity by measuring $M$ and $R_2$ values. The use of a low-dose insulin infusion rate (0.25 mU · kg$^{-1}$ · min$^{-1}$) aimed at partially suppressing the EGP for determination of hepatic insulin sensitivity.

As expected, subjects with mild-manifest diabetes demonstrate a decreased insulin response during OGTT, and this was more pronounced when related to the degree of glycemia (Table 1). In subjects with IGT, insulin secretion was enhanced, indicating that $\beta$-cells are not able to maintain NGT, despite hypersecretion of insulin. This is in accordance with our previous findings in similar patient groups (1). Others have demonstrated that a decreased first-phase insulin secretion has an impact on postprandial glucose homeostasis (13,30–32) and that restoration of an early increase in plasma insulin levels improves glucose tolerance caused by suppression of EGP (30). Thus, an adequate early insulin increase seems to be a prerequisite for the maintenance of normal postprandial glucose homeostasis.

As shown in Table 1, $M$ values were significantly lower in both IGT and diabetic patients compared with subjects with NGT. Strong correlations were obtained between $M$ values and LBM ($r = 0.49, P < 0.001$) and $V_{O_{2\max}}$ ($r = 0.37, P < 0.01$), suggesting a close relationship among body composition, physical fitness, and extrahepatic insulin sensitivity. Hence, peripheral insulin resistance is strongly related to phenotype characteristics.

Similar to what has been found in other studies, postabsorptive EGP was normal in patients with mild and moderate hyperglycemia (16,33–35). Thus, in all of these studies, increases in basal plasma glucose and insulin concentrations in patients were sufficient to overcome increases in postabsorptive EGP.

Several groups have evaluated glucose turnover during stepwise insulin clamps and found reduced hepatic and extrahepatic insulin sensitivity in subjects with IGT or type 2 diabetes (22,36–38). The suppression of hepatic glucose output during OGTT is also impaired in patients with IGT and type 2 diabetes. This defect plays a major role in contributing to postprandial hyperglycemia (12–14). MitraKou et al. (39) studied the extent to which abnormal muscle and liver glucose handling contributes to postprandial hyperglycemia in type 2 diabetes, by administering a continuous infusion of $^3$H-glucose and $^{1-13}$C-
glucose orally with a glucose load. They demonstrated that impaired suppression of endogenous hepatic glucose production and, to some extent, reduced splanchic glucose sequestration are the main factors responsible for postprandial hyperglycemia in type 2 diabetes. However, these studies do not allow evaluation of the contribution of insulin sensitivity in liver and extrahepatic tissue to postprandial glycemias. Therefore, in this study, we addressed this important issue. Notably, suppression of EGP during a low-dose insulin infusion (plasma insulin 240 ± 8 pmol/l, mean ± SE) explained 41% of the variation in glycemic responses during OGTT, whereas extrahepatic insulin sensitivity (Rd) and insulin response (only to a minor extent) independently contributed to the outcome of the model (Table 2). However, in a model, when replacing both Ra and Rd with other parameters for measuring extrahepatic insulin sensitivity (i.e., M value obtained during high-dose insulin infusion), it appeared that M value, insulin response, and age explained as much as 45% of the variation in glycemic response during OGTT (Table 3).

The above findings suggest that the insulin sensitivity of suppression of EGP is a most important determinant of whole-body glucose homeostasis during moderate and physiological increments in plasma glucose levels. Extrahepatic insulin sensitivity and insulin response seem to regulate plasma glucose response after OGTT, mainly by influencing EGP. This is also reflected by a close association between the magnitude of the suppression of the rate of Ra and the M values (r = 0.63, P < 0.001, data not shown) during low-dose insulin infusion. The ability of glucose per se to either suppress EGP or be uptaken in the liver during hyperglycemia (i.e., during an OGTT) was not determined in the present study, but this may be an additional regulator of postprandial glycemias. The impairment in the regulation of EGP by glucose per se (glucose effectiveness) has been observed in type 2 diabetic patients; it has presumably been caused by the failure of hyperglycemia at basal insulin levels to increase the flux through glucokinase and to inhibit flux through glucose-6-phosphatase (40).

Determinants of insulin sensitivity of suppression of EGP are not fully known. However, the present data demonstrate a close association between suppression of EGP and obesity and body composition, as evidenced from correlations between δ Ra and BMI (r = –0.31, P = 0.02) and δ Ra and LBM (r = 0.42, P = 0.0015). In general, suppression of EGP is thought to be mainly mediated via portal vein insulin delivery to the liver. Mittelman and coworkers (41, 42) have recently proposed that insulin-mediated suppression of EGP occurs mainly through suppression of adipocytes lipolysis. Other groups consider that suppression of EGP is regulated by both direct hepatic effect of portal insulin as well as indirect or extrahepatic effects of insulin (43–45).

In the present study, FFA levels were significantly higher in subjects with either IGT or type 2 diabetes at basal conditions and during insulin infusions. Although FFA turnover was not directly measured, it is reasonable to assume that an increased flux of FFAs contributed to the hepatic insulin resistance observed in these two groups of subjects. This assumption is confirmed in multiple stepwise regression analysis, demonstrating that FFA concentration, attained during the low-dose insulin infusion rate, explained 21% of the variation in δ R (data not shown). However, this also suggests that an impaired suppression of EGP in subjects with IGT and type 2 diabetes observed in this study is not solely caused by increased flux of FFAs but rather includes an impairment of transduction of insulin signal in liver. This is in agreement with a recent study of Lewis et al. (43). Direct evidence for the central role of liver in control of glucose homeostasis was recently provided in studies of mice, with liver- or muscle-specific insulin-receptor knockout (46, 47). The loss of direct insulin action in liver resulted in severe insulin resistance, glucose intolerance, hyperinsulinemia, and a failure of insulin to suppress EGP, despite an intact insulin signaling in adipocytes and muscle (46). In contrast, mice with severe insulin resistance in skeletal muscle, caused by muscle-specific insulin-receptor knockout, preserve whole-body glucose homeostasis (47).

An increase in glucagon or catecholamines could also have contributed to the observed differences in EGP in the present study, mainly through influences on glycogenolysis and gluconeogenesis (45). Glucagon levels were similar in all three study groups (data not shown), in whom catecholamines were not measured.

In summary, the present study suggests that an impaired insulin sensitivity of suppression of EGP is an early and important determinant of glucose intolerance in humans. In addition, insulin responsiveness and extrahepatic insulin sensitivity contribute to the variation in blood glucose response during OGTT.

ACKNOWLEDGMENTS

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