Prandial Glucose Effectiveness and Fasting Gluconeogenesis in Insulin-Resistant First-Degree Relatives of Patients With Type 2 Diabetes

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Impaired glucose effectiveness (i.e., a diminished ability of glucose per se to facilitate its own metabolism), increased gluconeogenesis, and endogenous glucose release are, together with insulin resistance and β-cell abnormalities, established features of type 2 diabetes. To explore aspects of the pathophysiology behind type 2 diabetes, we assessed in a group of healthy people prone to develop type 2 diabetes (n = 23), namely first-degree relatives of type 2 diabetic patients (FDR), *1*) endogenous glucose release and fasting gluconeogenesis measured using the ^2H_2O technique and *2*) glucose effectiveness. The FDR group was insulin resistant when compared with an age-, sex-, and BMI-matched control group without a family history of type 2 diabetes (n = 14) (M value, clamp: 6.07 ± 0.48 vs. 8.06 ± 0.69 mg · kg^{-1} lean body weight (lbw) · min^{-1}; P = 0.02). Fasting rates of gluconeogenesis (1.28 ± 0.06 vs. 1.41 ± 0.07 mg · kg^{-1} lbw · min^{-1}; FDR vs. control subjects, P = 0.18) did not differ in the two groups and accounted for 53 ± 2 and 60 ± 3% of total endogenous glucose release. Glucose effectiveness was examined using a combined somatostatin and insulin infusion (0.17 vs. 0.14 mU · kg^{-1} · min^{-1}, FDR vs. control subjects), the latter replacing serum insulin at near baseline levels. In addition, a 360-min labeled glucose infusion was given to simulate a prandial glucose profile. After glucose infusion, the integrated plasma glucose response above baseline (1817 ± 94 vs. 1789 ± 141 mmol/l per 6 h), the ability of glucose to simulate its own uptake (1.50 ± 0.13 vs. 1.32 ± 0.16 ml · kg^{-1} lbw · min^{-1}), and the ability of glucose per se to suppress endogenous glucose release did not differ between the FDR and control group. In conclusion, in contrast to overt type 2 diabetic patients, healthy people at high risk of developing type 2 diabetes are characterized by normal glucose effectiveness at near-basal insulinemia and normal fasting rates of gluconeogenesis. *Diabetes* 49:2135–2141, 2000

Type 2 diabetes is characterized by a large number of hormonal and metabolic abnormalities including insulin resistance, impaired glucose effectiveness, augmented gluconeogenesis, and disturbed islet cell secretion (1,2). An inherited component is strongly involved in the pathogenesis of the disease, but lifestyle and other environmental factors also contribute. Hence, it is estimated that the lifetime risk of developing type 2 diabetes is between 40 and 60% in first-degree relatives of type 2 diabetic patients (FDR) (3,4). Because the metabolic derangement in type 2 diabetes per se is able to induce hormonal and metabolic abnormalities, it is not possible to evaluate to what extent the aberrations in type 2 diabetic patients are of primary pathophysiological significance or if they merely reflect glucose toxicity. To circumvent this hindrance, healthy people at a substantial risk of developing type 2 diabetes, e.g., FDR, are often examined to cast light on mechanisms behind development of the disease.

Many studies report impaired insulin-stimulated glucose uptake in these healthy but potentially prediabetic individuals (4–11). In addition, an increasing number of studies have demonstrated, by using different experimental designs, defects in β-cell function (9–12). However, the function of other important regulators of glucose homeostasis are not well defined in FDR. Thus, gluconeogenesis, which contributes considerably to hyperglycemia in diabetes, has not been assessed nor has the ability of glucose to facilitate its own metabolism (i.e., to stimulate glucose uptake and suppress glucose release). That ability has attracted increasing interest, especially in insulin-resistant states, in which glucose effectiveness may play a pivotal compensatory role in promoting glucose uptake. In particular, it has been suggested, by using the frequently sampled intravenous glucose tolerance test (FSIGT) and the minimal model, that an increased glucose effectiveness may act as a compensatory mechanism maintaining normal glucose tolerance in insulin-resistant FDR (13). However, whereas FSIGT minimal model analysis provides estimates of insulin sensitivity comparable to those

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AUC, area under the curve; EGR, endogenous glucose release; FDR, first-degree relatives of type 2 diabetic patients; FFA, free fatty acid; FSIGT, frequently sampled intravenous glucose tolerance test; GE_b, net glucose effectiveness; GE_b*, index of the ability of glucose to stimulate its own uptake; GE_{liver}, index of the ability of glucose to suppress its own production; GIR, glucose infusion rate; HMT, hexamethylenetetramine; lbw, lean body weight; S_G, glucose effectiveness.

from the glucose clamp technique (14,15), recent studies have questioned the model's ability to accurately assess glucose effectiveness (16–19). To overcome these potential errors, an alternative approach was recently introduced (20,21). Briefly, during somatostatin infusion and baseline replacement of insulin (and glucagon and growth hormone), a prandial plasma glucose profile is simulated by a dynamic glucose infusion. Using the labeled exogenous glucose infusates, this model allows simultaneous assessment of glucose-mediated glucose uptake and endogenous glucose release and thus estimation of glucose effectiveness on both peripheral use and glucose production.

The present study was consequently undertaken to gain further insight into cardinal aspects of glucose metabolism in healthy relatives of type 2 diabetic individuals. The first step was to reappraise the ability of glucose to facilitate its own uptake and suppress its own production by using the above approach during constant (near)-baseline insulin concentrations and a dynamic glucose infusion simulating prandial glucose excursion. The second step was to determine whether gluconeogenesis is already abnormal in the prediabetic state. The latter was assessed by combining the isotope dilution method with the deuterated water technique to measure the fractional contribution of gluconeogenesis to glucose production (22,23).

RESEARCH DESIGN AND METHODS

Subjects. After approval from the Ethical Committee, County of Aarhus, 23 healthy FDR and 14 healthy subjects without any family history of diabetes gave written consent to participate in the study. All participants were Caucasian. Within the group of FDR, 5 had two first-degree relatives, 13 had one parent and two or more second-degree relatives, and 5 had only one parent with type 2 diabetes. The FDR and control subjects were from unrelated families, and the two groups were matched for age, sex, and BMI. All exhibited a normal oral glucose tolerance test (75 g glucose) according to World Health Organization criteria. The clinical data of the two groups are recorded in Table 1. None of the recruited subjects were taking any medication. At least 3 days before study, subjects were instructed not to engage in vigorous exercise.

Experimental design. All subjects underwent a hyperinsulinemic-euglycemic clamp and a prandial glucose infusion test; this test was preceded by a labeled water experiment. Examinations were separated by at least 2 weeks and were performed in random order.

Euglycemic-hyperinsulinemic clamp. After an overnight fast (from 2200), subjects were admitted to the clinical research center at 0730. At 0800, an 18-gauge cannula was inserted into a dorsal hand vein. The hand was then kept in a heated Plexiglas box (55°C) to allow sampling of arterialized venous blood. In addition, a cannula was placed in an antecubital vein to be used for infusions. After 90 min, an infusion of insulin at a rate of 0.6 mU · kg^{-1} · min^{-1} was started and maintained for 150 min. An infusion of 20% glucose was also started, and the infusion rate was adjusted to keep the plasma glucose concentration at ~5 mmol/l. The amount of glucose (milligrams per kilogram lean body weight [lbw] per minute) required to maintain euglycemia during the last 30 min of the clamp (i.e., time 120–150 min) was taken as an index of insulin action (*M* value).

Labeled water and prandial glucose infusion test. *S*ubjects were admitted to the clinical research center at 2200 on the evening before the study. A standard meal (carbohydrate content ~50%) was consumed between 1800 and 2000. At 0500, 0600, and 0700 on the following morning, the subjects drank 1.7 ml of ^2H_2O (99.9% H; Cambridge Isotope Laboratories, Andover, MA) per kilogram body water. Body water was calculated to be 50% of total body weight in women and 60% of total body weight in men. Water ingested ad libitum thereafter was enriched to 0.5% with ^2H_2O to maintain isotopic steady state. At 0730 (time, –150 min), a primed continuous infusion of [3-^{3}H]glucose (17 µCi prime, 0.17 µCi/min continuous) was started and continued to the end of the study to measure endogenous glucose release (EGR) and glucose disposal rate. During the prandial glucose infusion, the rate of continuous [3-^{3}H]glucose was changed to clamp specific activity (see below). Blood was collected at –60, –30, and 0 min to determine the fractional contribution of gluconeogenesis to EGR (Fig. 1).

TABLE 1
Subject characteristics

	FDR	Control subjects
Age (years)	34 ± 2	34 ± 2
Sex (M/F)	12/11	7/7
BMI (kg/m^2)	25.8 ± 0.5	25.0 ± 0.7
Waist-to-hip ratio	0.87 ± 0.01	0.86 ± 0.01
Lean body weight (% of body weight)	74 ± 2	73 ± 3
Fasting plasma glucose (mmol/l)	5.4 ± 0.1*	5.1 ± 0.0
Fasting serum insulin (pmol/l)	40 ± 4*	25 ± 2
M value (mg · kg^{-1} lbw · min^{-1})	6.07 ± 0.48	8.06 ± 0.69

Data are means ± SE. *P < 0.05.

A 6-h preprogrammed variable glucose infusion was started at time zero using an infusion pump (model PhD 2000, Harvard Apparatus, South Natick, MA), driven by a PC2/30 265 Computer (IBM, Rochester, MN). Glucose was infused in a manner (21) mimicking the systemic rate of appearance of glucose that occurs after ingestion of 50 g of glucose. The pattern and amount of glucose and tracer infused normalized to lean body mass was equal in the two groups. Furthermore, at time zero, an infusion containing somatostatin (Ferring, Kiel, Germany) (60 ng · kg^{-1} · min^{-1}), glucagon (Novo Nordisk, Bagsværd, Denmark) (time 0–120 min, 0.65 ng · kg^{-1} · min^{-1}; time 120–360 min, 1.30 ng · kg^{-1} · min^{-1}), and growth hormone (Novo Nordisk) (2 ng · kg^{-1} · min^{-1}) was also started. Finally, a constant basal insulin infusion (Insulin Actrapid; Novo Nordisk) was started at rates of 0.17 mU · kg^{-1} · min^{-1} in the FDR (n = 23) and at 0.14 mU · kg^{-1} · min^{-1} in the control subjects (n = 10). These basal insulin infusion rates were chosen based on previous experiments in which basal insulin concentrations were determined individually (20,24,25) and the fact that fasting insulin concentrations were expected to be higher in the FDR group because of insulin resistance. However, to assess glucose effectiveness during matched basal insulin concentrations in the control and FDR groups, an additional experiment was performed in the control subjects in which basal insulin was infused at 0.17 mU · kg^{-1} · min^{-1} (n = 13). The two experiments were done in random order.

In an effort to maintain constant specific activities during the experiments, the rate of basal [3-^{3}H]glucose was adjusted (time –150 to 0 min, 100%; 0–30 min, 70%; 30–60 min, 46%; 60–90 min, 55%; 90–120 min, 53%; 120–150 min, 58%; 150–210 min, 61%; and 210–360 min, 65%) according to the anticipated suppression of EGR during the glucose infusion. In addition, all glucose infusions contained [3-^{3}H]glucose (26). Hence, plasma glucose specific activity remained constant during the glucose infusion in both groups.

Analytical techniques. Arterialized plasma glucose samples were measured in duplicate immediately after sampling (Beckman Instruments, Palo Alto, CA). Samples for hormone analysis were placed on ice, centrifuged at 4°C, separated, and stored at –20°C until assay. Serum insulin was determined by two-site enzyme-linked immunosorbent assay (27). Plasma glucagon, serum growth hormone, and C-peptide concentrations were measured by radioimmunoassay. Serum free fatty acids (FFAs) were measured enzymatically using a Wako NEFA (nonesterified fatty acid) Test Kit (Wako Chemicals, Neuss, Germany).

The measurement of deuterium enrichment on carbon 2 and 5 in glucose was performed as previously described (23). Briefly, 15 ml blood was diluted with 30 ml demineralized water and deproteinized using 15 ml of 0.3N $ZnSO_4$ and 15 ml of 0.3N $Ba(OH)_2$. The samples were centrifuged at 2,000 rpm for 15 min, and the pellet was diluted in 15 ml demineralized water to wash out the remaining glucose. Glucose was isolated by successive ion-exchange chromatography and high-performance liquid chromatography. For determination of deuterium enrichment on C5, glucose was first converted to xylose, and the carbon 5 of glucose with its hydrogens was cleaved by periodate oxidation to formaldehyde, which was condensed with ammonium hydroxide to form hexamethylenetetramine (HMT). The ^{2}H bound to C2 of glucose was isolated after conversion of glucose to ribitol-5-phosphate and arabitol-5-phosphate and treated to form HMT. HMT was analyzed on a Hewlett-Packard mass spectrometry system. Standard solutions of glucose of known enrichment were run along with the unknown samples to calibrate for instrument variations.

Calculation of glucose turnover. Glucose appearance and disappearance were calculated using Steele' s equations for non–steady state (28) after smoothing of glucose specific activity using the method of Bradley et al. (29). EGR was determined by subtracting the glucose infusion rate from the tracer-determined rate of glucose appearance. The fractional contribution of gluco-

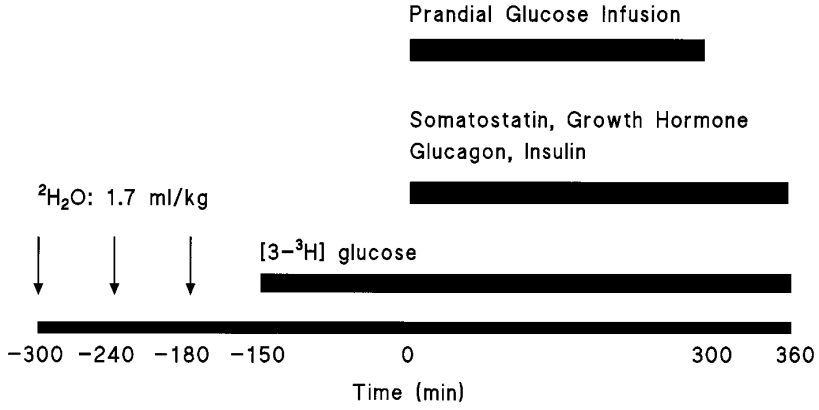

FIG. 1. Experimental design as described in the text.

neogenesis to glucose production equals the ratio between deuterium bound to carbon 5 in glucose to that bound to carbon 2 (23). A quantitative estimate of baseline gluconeogenesis was determined by multiplying the mean EGR from time –30 to 0 min by the mean of the fractional contribution from time –60 to 0 min.

Assessment of glucose effectiveness from area under the curve calculations. The calculations of the three indexes of glucose effectiveness—net glucose effectiveness (GE_b), index of the ability of glucose to stimulate its own uptake (GE_b*), and index of the ability of glucose to suppress its own production (GE_{liver})—from plasma glucose and tracer concentrations have been described in detail elsewhere (20). Net glucose effectiveness at basal insulinemia, i.e., the combined effect of glucose to suppress its own production and stimulate its own uptake (GE_b) was calculated as the ratio between the area under the curve (AUC) of the exogenous glucose infusion rate (GIR) and the AUC of the glucose concentration above basal (ΔG):

$$GE_b = \frac{AUC\ [GIR(t)]}{AUC\ [\Delta G(t)]} \times (ml \cdot kg^{-1}\ lbw \cdot min^{-1})$$

Because equal amounts of glucose were infused in the groups, the excursion of glucose concentration above basal was inversely related to net glucose effectiveness in the two groups. The greater the glycemic excursion, the lower the net glucose effectiveness (GE_b). Disposal glucose effectiveness, i.e., the ability of glucose to stimulate its own uptake (GE_b*), was also calculated as described by Basu et al. (20):

$$GE_b^* = \frac{\{AUC\ [\Delta GIR^*(t)] - PCR_b\ G_b\ AUC\ [\Delta SA(t)]\}}{\{AUC\ [\Delta G^*(t)] - G_b\ AUC\ [\Delta SA(t)]\}} \times (ml \cdot kg^{-1}\ lbw \cdot min^{-1})$$

where ΔGIR* is the tracer infusion rate above the basal rate, ΔG* is tracer glucose concentration, SA is the tracer specific activity, G_b is the baseline glucose concentration, and PCR_b is the basal plasma glucose clearance rate. Δ Denotes the excursion of each variable above basal. Finally, the effect of glucose on EGR (GE_{liver}, ml · kg^{-1} lbw · min^{-1}) was calculated by subtracting GE_b* from net glucose effectiveness (GE_b).

Statistical analysis. Data in the text and figures are expressed as means ± SE. All rates and indexes are expressed per kilogram lean body weight. Responses above or below baseline were calculated using the trapezoidal rule. Basal is defined as the mean of the values present during the 30 min before the prandial glucose infusion. Nonpaired Student's *t* test was used for statistical comparison between FDR and control subjects (either 0.14 or 0.17 mU · kg^{-1} · min^{-1}). A *P* value <5% was considered statistically significant.

RESULTS

Fasting glucose and hormone concentrations and insulin sensitivity. After overnight fasting, plasma glucose (5.4 ± 0.1 vs. 5.1 ± 0.1 mmol/l; $P = 0.02$), serum insulin (40 ± 5 vs. 25 ± 2 pmol/l; $P = 0.02$), and C-peptide (509 ± 29 vs. 434 ± 18 pmol/l; $P = 0.07$) concentrations were higher in FDR than in control subjects. Fasting plasma glucagon (49 ± 4 vs. 53 ± 6 ng/l; $P = 0.55$) and serum growth hormone (0.3 ± 0.1 vs. 1.2 ± 0.9 μg/l; $P = 0.22$) concentrations were similar in the two groups.

The amount of glucose required to maintain euglycemia during the hyperinsulinemic clamp was lower in the FDR than in control subjects (6.07 ± 0.48 vs. 8.06 ± 0.69 mg · kg^{-1} lbw · min^{-1}; $P = 0.02$), indicating the presence of insulin resistance in the former group. There was no relationship between insulin sensitivity and family history of diabetes.

Fasting endogenous glucose release and gluconeogenesis. Rates of EGR (2.40 ± 0.06 vs. 2.37 ± 0.10 mg · kg^{-1} lbw · min^{-1}; $P = 0.79$) and gluconeogenesis (1.28 ± 0.06 vs. 1.41 ± 0.07 mg · kg^{-1} lbw · min^{-1}; $P = 0.18$) did not differ between groups despite elevated circulating insulin concentrations in the FDR. Gluconeogenesis accounted for 53 ± 2 and 60 ± 3% of total EGR in the FDR and control subjects, respectively (Fig. 2).

Substrate and hormone concentrations during prandial glucose infusion. During basal insulin infusion (0.17 vs. 0.14 mU · kg^{-1} · min^{-1}, FDR vs. control subjects), average serum insulin concentrations (time 0–360 min) were higher in FDR than in control subjects (66 ± 4 vs. 54 ± 4 pmol/l; $P = 0.03$). As expected, circulating insulin concentrations did not differ in the two groups when applying identical infusion

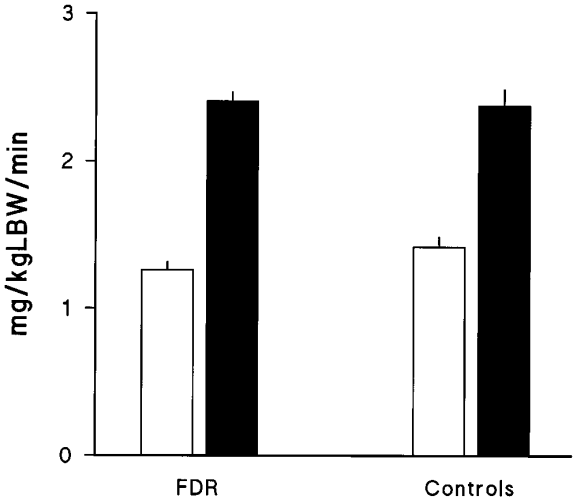

FIG. 2. Fasting rates of EGR (■) and gluconeogenesis (□) in FDR and control subjects. Gluconeogenesis was calculated by multiplying the mean ratio of deuterium enrichment at carbon 5 to that at carbon 2 in glucose by the mean rate of fasting EGR from –60 to 0 min.

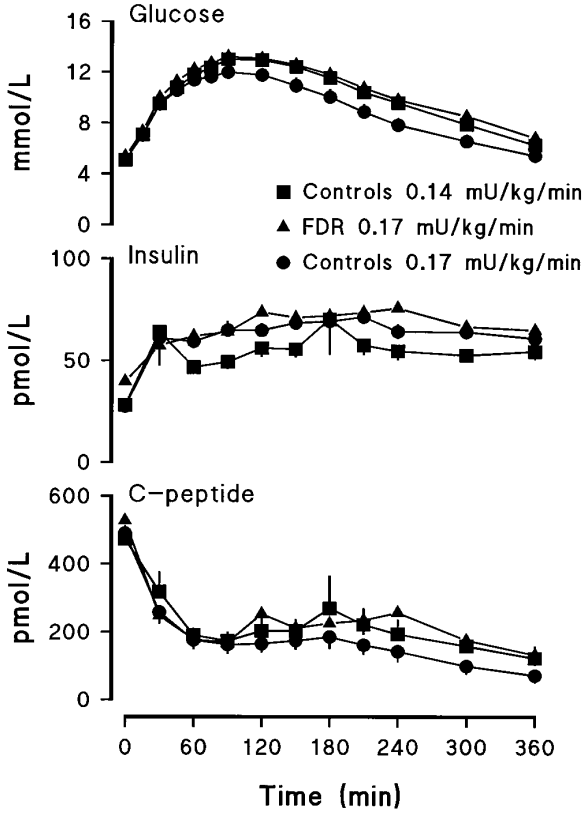

FIG. 3. Plasma glucose, serum insulin, and C-peptide concentrations in the FDR and control subjects during the prandial glucose infusion. The glucose infusion was started at 0 min.

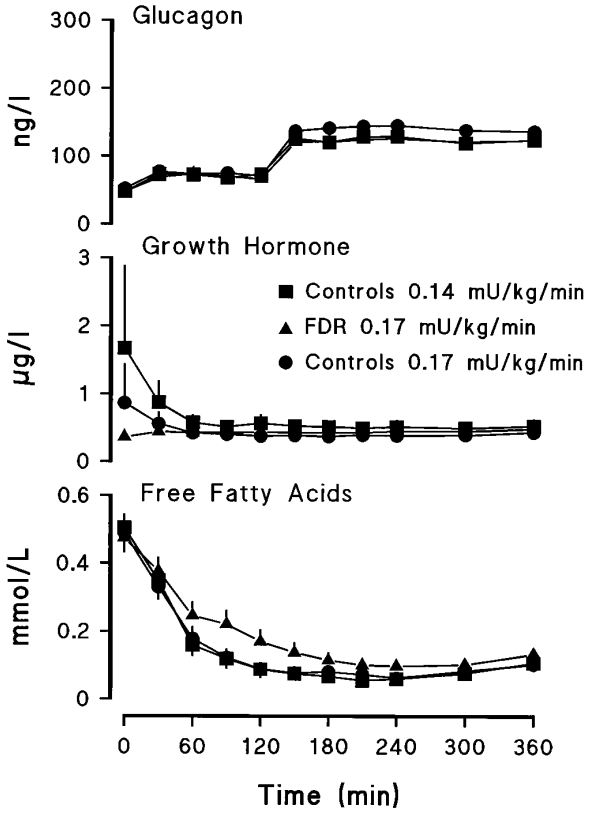

FIG. 4. Plasma glucagon, serum growth hormone, and FFA concentrations in the FDR and control subjects during the prandial glucose infusion. The glucose infusion was started at 0 min.

rates (0.17 mU · kg^{-1} · min^{-1}) (66 ± 4 vs. 61 ± 3 pmol/l; P = 0.58). During somatostatin infusion, C-peptide concentrations were equally suppressed (76 ± 12 vs. 79 ± 10 vs. 60 ± 8 pmol/l per 6 h, FDR vs. control subjects [0.14 mU · kg^{-1} · min^{-1}]) versus control subjects (0.17 mU · kg^{-1} · min^{-1}), indicating comparable inhibition of endogenous insulin secretion during glucose infusion. Plasma glucagon (104 ± 10 vs. 102 ± 7 vs. 114 ± 4 ng/l) and growth hormone (0.41 ± 0.4 vs. 0.55 ± 0.10 vs. 0.43 ± 0.03 μg/l) concentrations did not differ during the three examinations. All hormone concentrations remained constant and equal during glucose infusion. Serum FFA concentrations declined promptly after insulin and glucose infusion and remained equally suppressed in the FDR and control subjects (62 ± 9 vs. 45 ± 7 vs. 46 ± 8 mmol/l per 6 h) (Figs. 3 and 4).

Estimates of glucose effectiveness. After initiation of the prandial glucose infusion, the glycemic excursion did not differ in control subjects (0.14 mU · kg^{-1} · min^{-1}) and FDR, whether measured as peak plasma glucose concentration (13.3 ± 0.4 vs. 13.4 ± 0.2 mmol/l; P = 0.71) or integrated response above baseline (1,789 ± 141 vs. 1,817 ± 94 mmol/l per 6 h; P = 0.87), indicating that net glucose effectiveness (see below) was similar in the two groups. During the higher insulin infusion rate in control subjects (0.17 mU · kg^{-1} · min^{-1}), peak plasma glucose (12.2 ± 0.5 vs. 13.4 ± 0.2 mmol/l; P = 0.01) as well as the glycemic excursion above baseline (1,408 ± 153 vs. 1,817 ± 94 mg/kg per 6 h; P = 0.02) was lower in the control subjects than in the FDR (Figs. 3, 5, and 6).

GE_b was almost identical in control subjects (0.14 mU · kg^{-1} · min^{-1}) and FDR (2.59 ± 0.17 vs. 2.61 ± 0.25 ml · kg^{-1} lbw · min^{-1}; P = 0.94) during basal insulinemia. However, when control subjects were infused with insulin at an rate equivalent to that of FDR (0.17 mU · kg^{-1} · min^{-1}), GE_b was higher in the control subjects (3.84 ± 0.56 ml · kg^{-1} lbw · min^{-1}) compared with the FDR (P < 0.01). Neither GE_b* (the ability of glucose to stimulate its own uptake) (1.32 ± 0.16 vs. 1.50 ± 0.13 ml · kg^{-1} lbw · min^{-1}, control subjects vs. FDR, P = 0.42) nor the effect of glucose to suppress glucose production (GE_{liver}) (1.3 ± 0.3 vs. 1.1 ± 0.2 ml · kg^{-1} lbw · min^{-1}, control subjects vs. FDR, P = 0.49) differed between the two groups during near-basal insulinemia. Furthermore, the dynamic alterations of EGR during hyperglycemia were comparably suppressed in the groups (P = 0.88). Of note, plasma [3-^{3}H]glucose specific activity was maintained within ~10% of basal values in all experiments (Fig.5).

DISCUSSION

The present study explores two important aspects of glucose metabolism in FDR, i.e., people at risk of developing type 2 diabetes. First, it demonstrates that fasting gluconeogenesis and the ability of glucose per se to restrain EGR are unaltered in FDR and a matched control group. Second, it demonstrates that glucose effectiveness, as assessed by the labeled glucose infusate technique during a dynamic glucose infusion mimicking the systemic rate of appearance of glucose that occurs after ingestion of 50 g glucose, is similar in FDR and control subjects at near-basal insulinemia.

In type 2 diabetes, glucose production is inappropriately high for the prevailing glucose and insulin concentrations (30–32). Using different techniques, both animal and human

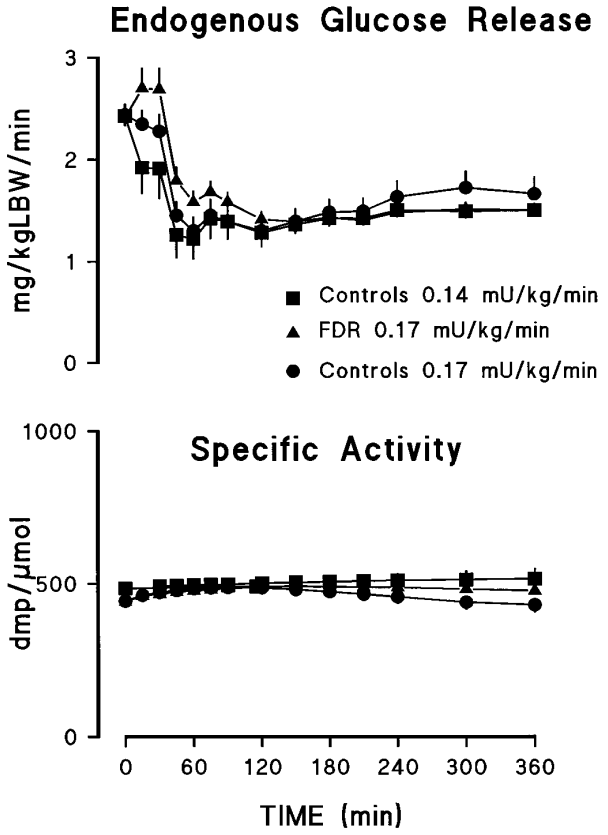

FIG. 5. Endogenous glucose release and [3-^{3}H]glucose specific activity in the FDR and control subjects before and during the prandial glucose infusion. The glucose infusion was started at 0 min.

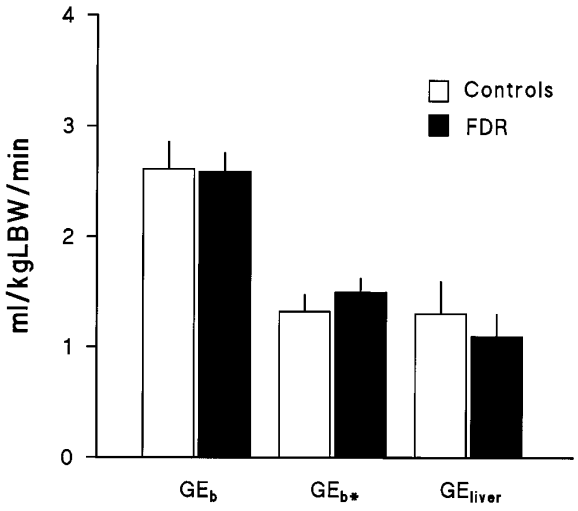

FIG. 6. Estimates of glucose effectiveness determined during near-basal insulin concentrations in FDR and control subjects. Insulin infusion rates were 0.17 vs. 0.14 mU · kg^{-1} · min^{-1}, respectively. GE$_b$ constitutes the combined effects of glucose to stimulate its own uptake (GE$_b$*) and suppress its own production (Ge$_{liver}$).

studies indicate that diabetes is associated with markedly increased rates of gluconeogenesis (33–36). However, to our knowledge, rates of gluconeogenesis have never been determined in healthy FDR. In the present study, the deuterated water technique (22,23) was applied to assess gluconeogenesis in the fasting state. Deuterated water was ingested after an ~12-h fast to minimize incorporation into glycogen. The fractional contribution of gluconeogenesis to EGR was determined as the ratio of ^{2}H in position 5 in glucose to that of ^{2}H in position 2 of glucose. Postabsorptive rates of gluconeogenesis were calculated by multiplying this rate by EGR.

Not only fasting EGR but also rates of fasting gluconeogenesis were similar in the two groups. Of notice is that comparable gluconeogenesis and consequently rates of glycogenolysis between groups are present under the condition of elevated insulinemia in FDR, suggesting hepatic insulin resistance. The kidneys contribute little EGR after 12 h of fasting (37). The presence of normal rates and fractions of gluconeogenesis in FDR suggests, but does not prove, that the increased gluconeogenesis in type 2 diabetes is secondary to the metabolic derangement and is not an inherited phenomenon. To some extent, the increase could be ascribed to the glucagon excess in type 2 diabetes. However, our FDR exhibited normal fasting plasma glucagon levels, in accordance with recent data demonstrating normal diurnal concentrations of glucagon in offspring of type 2 diabetic patients (11). On the other hand, one could reason that possible and discrete inherited abnormalities in hepatic glucose handling in FDR are balanced by compensatory insulin hypersecretion in contrast to overt type 2 diabetic individuals with more limited β-cell capacity.

In addition to hormones, nonhormonal factors regulate EGR. Glucose per se is a potent suppressor of hepatic glucose release (38,39). Both in vivo and in vitro studies indicate that glucose can decrease EGR as much as 60–90% (40). After an overnight fast, this action of glucose is mainly believed to be mediated via inhibition of net hepatic glycogenolysis through reduction of glycogen phosphorylase flux (41). The current study clearly demonstrates that the restraining effect of a prandial glucose profile on EGR is normal in FDR. After glucose infusion, EGR was again equally suppressed in the groups, suggesting that hepatic insulin resistance, rather than a reduced ability of hyperglycemia to suppress EGR, constitutes the main defect in the regulation of hepatic glucose metabolism in FDR.

Permissive amounts of insulin are required for glucose to suppress EGR (42,43). As in previous experiments (20,24,42), we aimed in our primary design to maintain a near-baseline insulin concentration during somatostatin infusion by replacement of insulin at different doses in FDR and control subjects (0.17 vs. 0.14 mU · kg^{-1} · min^{-1}, respectively). In both groups, circulating peripheral insulin concentrations were ~25 pmol/l higher during the pancreatic clamp than during fasting. With an almost zero endogenous insulin secretion, this is presumably equivalent to normal fasting insulin concentrations in the portal vein. It should be emphasized that the difference in the observed fasting serum insulin concentrations between the two groups was preserved during pancreatic clamping (15 vs. 12 pmol/l). Finally, these data are in accordance with recent studies in which dose dependency of glucose to decrease EGR (and gluconeogenesis) within the physiological area of glucose was found to be comparable in type 2 diabetic and nondiabetic individuals (42,44). Because of possible incorporation of ^{2}H from ^2H_2O into glycogen during glucose infusion, the present design did not allow us to reliably assess gluconeogenesis during prandial hyperglycemia.

The second important issue examined in the current study was the ability of glucose to promote its own uptake. After meal ingestion, the rate at which glucose is normalized is determined by the combined effects of insulin action and glucose effectiveness. Whereas FDR are characterized by insulin resistance, it is unclear whether glucose effectiveness also is altered in these individuals. This is a cardinal question because approximately half of the decline in plasma glucose concentration after glucose administration in healthy individuals has been suggested to be due to the mass action effect of hyperglycemia (45).

The classic FSIGT, without concomitant tracer injection, has proven useful in the measurement of insulin action, but its ability to accurately measure glucose effectiveness is less clear. It has been demonstrated (17–19) that the cold minimal model results in an overestimation of net glucose effectiveness when assessed in the presence of rapidly changing glucose and insulin concentrations.

Consequently, in the present experiment, glucose effectiveness was determined using an optimized minimal model independent protocol in which constant near-basal circulating insulin concentrations were maintained during glucose infusions, simulating a meal (20,21). Near-basal insulin concentrations were achieved by infusing insulin (concomitant with somatostatin) at rates of primarily 0.14 $mU \cdot kg^{-1} \cdot min^{-1}$ in the control group and 0.17 $mU \cdot kg^{-1} \cdot min^{-1}$ in the FDR. The rationale for using these infusion rates has been mentioned above. Whereas the difference in serum insulin between control subjects and FDR was maintained and portal insulin levels probably were replaced at basal levels, the insulin infusion rates were accompanied by a doubling of peripheral serum insulin concentrations. This difference may seem dramatic, but the average circulating concentrations were still well below 81 pmol/l—the upper limit for fasting lean individuals. Furthermore, without endogenous insulin secretion, an elevated peripheral insulin level is mandatory to balance hepatic metabolism. The insulin levels denoted near-basal are lower than those achieved by other models, apart from studies using non–insulin mediated glucose uptake with zero insulin (46).

During glucose infusion, plasma glucose concentrations increased equally in the two groups, suggesting that glucose effectiveness was similar in FDR and control subjects. This was equally evident whether glucose effectiveness was measured directly as the glycemic excursion above basal or whether GE_b and GE_b* were calculated. As a consequence of the primary design, basal serum insulin concentrations were higher in the FDR than in the control subjects. This result is in contrast to some studies that have examined glucose effectiveness in FDR, and it could be reasoned that the difference in insulin replacement between the groups might affect our estimate of effectiveness. To address this question, insulin replacement in the control group was also administered with an insulin infusion rate identical to that of FDR (0.17 $mU \cdot kg^{-1} \cdot min^{-1}$). This replacement resulted in higher estimates of GE* in the control subjects. On the basis of these data, a decreased glucose effectiveness in FDR, as demonstrated in a previous report (4), could be claimed. However, it is unlikely that this difference reflects dissimilarity in glucose effectiveness per se but rather is a result of an increased insulin action in control subjects compared with FDR. Glucose effectiveness constitutes the ability of glucose at basal circulating insulin concentrations to regulate its own metabolism. Basal serum insulin concentrations refer to the concentrations required to obtain identical biologic effects in the two groups, which by definition are higher in insulin-resistant FDR than in control subjects, to compensate for a reduced insulin sensitivity in the former.

Thus, the present study indicates that glucose effectiveness is unaltered in FDR and suggests that insulin resistance precedes the development of impaired glucose effectiveness in frank type 2 diabetes. Our study confirms data by Osei et al. (47) but is in conflict with Henriksen et al. (13), who by using cold minimal model analysis (FSIGT) reported increased glucose effectiveness in FDR and proposed that this could be a protective response in people prone to develop type 2 diabetes. Apart from differences in study design, the discrepancy between the results of the latter study and ours are difficult to resolve. However, the rapidly changing glucose and insulin concentrations could possibly result in an overestimation of the FSIGT variable glucose effectiveness (S_G) in insulin-resistant FDR. Our data may at first glance also seem in contrast with the study of Martin et al. (4), who found S_G to be decreased in FDR who later developed type 2 diabetes, again using the minimal model. However, insulinemia was similar in the prediabetic FDR compared with subjects who remained normoglycemic, and their results can thus be extrapolated to our data when applying identical insulin infusion rates in FDR and control subjects.

Although knowledge of the mechanisms behind the ability of glucose to promote its own uptake are still only rudimentary, an increase in glucose concentration stimulates translocation of GLUT4 transporters to the plasma membrane in muscle (48), similar to the actions of insulin and contraction on the GLUT4 transporters (49). This result could contribute to the disturbed glucose effectiveness in overt type 2 diabetes, although our data conceivably indicate that this aspect of the deranged metabolism is acquired.

In conclusion, the present study demonstrates that glucose effectiveness, as assessed during a prandial simulated plasma glucose profile in the presence of near-basal circulating insulin concentrations, is normal in FDR. This conclusion is evident regardless of whether glucose effectiveness is assessed as the glycemic increment above basal during glucose infusion or whether cold and hot indexes of minimal model parameters are determined. This study also demonstrates that fasting endogenous glucose release and gluconeogenesis are unaltered in slightly hyperinsulinemic FDR and that hyperglycemia per se restrains endogenous glucose release equally in both groups. Taken together, our results suggest that insulin resistance is the key defect in hepatic and muscle glucose metabolism in glucose-tolerant FDR.

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