Improvement of Insulin-Induced Glucose Disposal in Obese Patients With NIDDM After 1-Wk Treatment With *d*-Fenfluramine

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Objective: To study the short-term effects of the serotoninergic anorectic drug *d*-fenfluramine on insulin-induced glucose disposal. Research Design and Methods: A randomized double-blind placebo-controlled crossover trial with 1-wk treatment periods (2 × 15 mg/day *d*-fenfluramine) was conducted. Twenty obese subjects, 10 with normal oral glucose tolerance and 10 with non-insulin-dependent diabetes mellitus (NIDDM), were all treated with a weight-maintaining diet. Euglycemic-hyperinsulinemic glucose clamps with measurement of glucose kinetics with D-[3-^{3}H]glucose were performed at either two (patients without NIDDM, 0.05 and 0.10 U · kg^{-1} · h^{-1}) or three (patients with NIDDM, 0.05, 0.10, and 0.50 U · kg^{-1} · h^{-1}) insulin delivery rates. Results: In the nondiabetic subjects, no significant changes in any metabolic or hormonal parameter were measured in the basal state or during the clamp despite a slight reduction in body weight (−1.2 ± 0.5 kg, $P < 0.05$). In the diabetic patients, no significant changes in body weight or basal plasma insulin levels were observed, but fasting blood glucose levels (8.0 ± 0.8 vs. 9.4 ± 1.1 mM, $P < 0.005$) and plasma free fatty acid concentrations (1150 ± 227 vs. 1640 ± 184 μM, $P < 0.05$) were significantly reduced after *d*-fenfluramine compared with placebo. During the clamp, insulin metabolic clearance rate (MCR) was similar after both placebo and *d*-fenfluramine; endogenous (hepatic) glucose production was similarly and almost completely suppressed, whereas glucose disposal was remarkably enhanced after *d*-fenfluramine (average increase of glucose MCR 35 ± 12%, $P < 0.02$). Conclusions: Whatever the mechanism(s) involved, a 1-wk treatment with *d*-fenfluramine induces better blood glucose control and improves insulin sensitivity in obese patients with NIDDM independent of significant weight reduction; this last effect is not present in obese subjects with normal oral glucose tolerance. *Diabetes Care* 14:325–32, 1991

Fenfluramine is an anorectic pharmaceutical compound widely used for inducing weight loss. Its main mechanism of action involves serotoninergic activation in the brain, although additional peripheral effects are likely (1). There is evidence that fenfluramine improves insulin action in vitro and in vivo (2). In humans, fenfluramine has been shown to improve the glycemic control in obese glucose-intolerant subjects and in non-insulin-dependent diabetic (NIDDM) patients (3–5), independent of the effects of the drug on food intake and body weight (6). This action has been attributed to an increase in insulin sensitivity rather than an increase in insulin secretion, because lower glucose values were observed in the presence of lower insulin levels (3–6). Only one study more directly measured insulin sensitivity in humans via the euglycemic-hyperinsulinemic clamp technique; it confirmed that a chronic treatment with fenfluramine enhanced the insulin-induced peripheral glucose disposal in sulfonylurea-treated NIDDM patients in the absence of significant weight loss (7). However, in rats, glucose-turnover measurements showed that the improvement of insulin action, although also present at the peripheral tissues, appeared to predominate at the hepatic site (8).

This study aimed at investigating the effects of a 1-wk treatment with *d*-fenfluramine, the dextrostereoisomer that is a pure serotoninergic agonist (9), on insulin sen-

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sitivity in obese subjects with normal oral glucose tolerance and in obese patients with moderate NIDDM treated with diet alone. The protocol, designed as double blind, randomized, and crossover versus placebo, used the classic euglycemic-hyperinsulinemic glucose clamp at various insulin infusion rates combined with isotopic measurement of glucose kinetics. To avoid interference due to body-weight changes, the subjects followed a weight-maintaining diet, and the period of treatment was limited to 1 wk.

RESEARCH DESIGN AND METHODS

Twenty obese patients with a body mass index ranging between 28.7 and 36.9 kg/m^2 gave their informed consent for participation in the study. Their clinical characteristics are summarized in Table 1. Ten patients had normal oral glucose tolerance and 10 had NIDDM according to the National Diabetes Data Group criteria (10). The nondiabetic obese subjects had basal plasma insulin levels in the upper limit of the normal range. The diabetic patients had significantly increased fasting blood glucose levels despite basal hyperinsulinemia; they had a similar body weight excess but were significantly older than the nondiabetic obese subjects. Their HbA_{1c} levels averaged 7.2 ± 0.5% (mean ± SD, 4.6 ± 0.6%). No subject was taking any drug for at least 2 wk before starting the study. All were consuming a regular weight-maintaining diet, which was followed throughout the study.

The study was approved by the ethical committee of the University of Liège, Belgium. An initial 15-day run-in period during which the patients were examined at 1-wk intervals allowed for verification that body weight and fasting blood glucose levels remained stable. Thereafter, the patients were treated during 1 wk with either 2 × 15 mg/day *d*-fenfluramine (Isomeride, Servier, Neuilly, France) or placebo; a 2- to 3-wk washout period was allowed between the two treatment periods. In each group, five patients were given placebo and the remaining five were given *d*-fenfluramine. Drug compliance was verified by interview and pill count at the end of each treatment period. The patients were admitted to the metabolic ward at the end of each week of treatment at 0800 after a 12-h overnight fast. After ingesting their last drug capsule (*d*-fenfluramine or placebo), they were given bed rest and maintained supine throughout the experiment. Eighteen-gauge polyethylene catheters were inserted in an antecubital vein in each arm; one was used for all infusions, and the other permitted insertion of a double-lumen catheter for continuous blood withdrawal with the Biostator (Life Science, Miles, Elkhart, IN). A superficial dorsal hand vein was cannulated in anterograde fashion with a 19-gauge butterfly needle and kept patent by a slow infusion of 0.9% NaCl; the hand was kept warm by an electric lamp for intermittent sampling of partially arterialized venous blood.

To quantify the rate of glucose appearance (R_a) and the rate of overall glucose disappearance (R_d), a primed (20 μCi) continuous (0.2 μCi · min^{-1}) infusion of D-[3-^{3}H]glucose (Du Pont-NEN, Boston, MA; 11.5 Ci × mmol^{-1}; verified to be 100% pure by high-performance liquid chromatography) dissolved in 0.9% NaCl was infused with a high-precision pump (Hoechst, Frankfurt, Germany). At least 2 h were allowed for isotopic equilibration. Afterward, each subject was submitted to a euglycemic-hyperinsulinemic glucose clamp as described by DeFronzo et al. (11) and applied to the Biostator by Verdonk et al. (12). Two insulin delivery rates of 2 h each were administered in both groups (0.05 and 0.10 U · kg^{-1} · h^{-1}). In addition, the diabetic obese patients received a third 2-h insulin infusion at a rate of 0.50 U · kg^{-1} · h^{-1}. Human insulin (Actrapid HM, Novo, Copenhagen) was dissolved in 0.9% NaCl containing 0.3 g × 100 ml^{-1} human serum albumin (Institut Merieux, Lyon, France). Glucose was infused as a 30% solution to which 0.26 meq KCl × ml^{-1} was added to prevent hypokalemia.

Plasma glucose was clamped at ~5 mM in the euglycemic nondiabetic obese subjects. In the diabetic obese patients, plasma glucose levels were clamped at the basal level in five patients (~7 mM), whereas in the five others, the higher initial plasma glucose concentrations (~12 mM) had to first be progressively decreased to this target level with a primary insulin infusion before beginning the clamp in both experimental conditions. An interval of at least 45 min without insulin was observed before starting the glucose clamp in each test.

Blood samples for the various determinations were collected at the times indicated (Figs. 1–4). Except for plasma glucose, which was determined immediately after the experiment by the hexokinase method (Auto-Analyzer II, Technicon, Tarrytown, NY), all other blood samples for substrates, hormones, and R_a-R_d determi-

TABLE 1
Main characteristics of the subjects

	Sex (F/M)	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Fasting blood glucose (mM)	Fasting plasma insulin (pM)
Nondiabetic obese	7/3	40 ± 4	166 ± 3	91.6 ± 4.4	33.2 ± 2.7	4.4 ± 0.2	83 ± 11
NIDDM obese	4/6	52 ± 3	165 ± 3	89.1 ± 2.7	32.8 ± 0.8	9.4 ± 1.0	195 ± 34

Values are means ± SE. BMI, body mass index; NIDDM, non-insulin-dependent diabetes mellitus. n = 10 for both groups. $P < 0.05$, $P < 0.001$, $P < 0.01$, for age, fasting blood glucose, and fasting plasma insulin, respectively; all others NS.

nations were centrifuged after each experiment, and plasma was stored at −20°C until assay. Plasma [3-^{3}H]glucose specific activity was determined as reported elsewhere (13). Plasma insulin (14), glucagon (15), C-peptide (16), cortisol (17), and β-endorphin (18) were all determined by radioimmunoassay methods. Plasma glycerol (19) and free fatty acid (FFA; 20) were measured by enzymatic procedures. All samples obtained during both experiments in each subject were assayed within the same series to eliminate interassay variations. HbA_{1c} levels were measured with an isofocusing method (21).

Calculations and statistical analysis. The amount of glucose infused necessary to maintain blood glucose at its determined level despite insulin infusion (glucose infusion rate [GIR]) was calculated for 20-min intervals throughout the experiment and expressed as mg · kg^{-1} · min^{-1}. R_a and R_d were calculated from 20-min integrated [^{3}H]glucose data (13) with Steele's equations (22) in their derivative forms for non-steady-state conditions. Endogenous glucose production (EGP) was calculated by subtracting GIR from R_a; negative numbers for EGP were observed in some patients at the various insulin-clamp steps. As demonstrated on theoretical and experimental grounds, such underestimation of glucose turnover by the tracer method is largely accounted for by a model error emerging at high rates of glucose metabolism (23). Because a simple and satisfactory correction for changes in the glucose system during the non–steady state is not yet available, along with others, we took the negative numbers to indicate a nil EGP (24). Metabolic clearance rate (MCR) of glucose was calculated by dividing R_d by steady plasma glucose levels during the same time intervals. The MCR of insulin during the clamp was calculated as previously described with plasma insulin and C-peptide levels (25). Note that, in the diabetic obese group, glucose-kinetics evaluation performed at time 0 did not reflect true basal data because five diabetic patients already required insulin infusion to lower their blood glucose levels before beginning the clamp. In the nondiabetic obese group, one experiment had to be stopped after the first 120 min of the clamp due to technical problems with the double-lumen catheter. Consequently, in this group, the results from 10 subjects were analyzed for the first insulin delivery rate and from 9 subjects for the second insulin level.

All data were expressed as means ± SE. After preliminary analysis of variance, statistical comparisons between each modality of treatment were performed by paired Student's *t* test analysis. Response curves during the glucose clamps were compared by applying Zerbe's method (26) for each variable. This method allows comparison of response curves not only pointwise but also over any fixed period—in this study, the 120-min period corresponding to each insulin delivery rate—thus providing a global assessment of the differences between placebo and *d*-fenfluramine treatments. An *F* criterion was calculated to test the hypothesis of equal mean response curves between the two experimental conditions. Coefficients of correlation were calculated with Pearson's *r*. All results were considered significant at $P < 0.05$

RESULTS

In nondiabetic obese patients, a slight, although significant, body-weight reduction occurred during the 1-wk treatment with *d*-fenfluramine (Table 2). Nevertheless, fasting blood glucose and plasma insulin levels did not change significantly. Glucose kinetics data during the two insulin infusion rates of the glucose clamp are illustrated in Fig. 1. Basal levels of plasma glucose, R_a, R_d, and MCR of glucose were similar after *d*-fenfluramine and placebo. Plasma glucose levels were clamped at ~5 mM with a mean coefficient of variation of 5 ± 1% in both tests. During insulin infusion, GIR, R_a, R_d, and MCR of glucose were similarly increased, whereas EGP fell to near 0 after treatment with either *d*-fenfluramine or placebo.

Changes in hormones and substrates are detailed in Fig. 2. No significant differences were observed in plasma insulin, C-peptide, and glucagon concentrations be-

TABLE 2
Basal evaluation before the glucose clamp in both experimental conditions and changes during each 1-wk period of treatment with either *d*-fenfluramine or placebo

	Body weight (kg)		Blood glucose (mM)		Plasma insulin (pM)	
	Placebo	*d*-Fenfluramine	Placebo	*d*-Fenfluramine	Placebo	*d*-Fenfluramine
Nondiabetic obese						
Basal	91.1 ± 4.0	90.0 ± 3.8*	4.2 ± 0.1	4.2 ± 0.1	65 ± 9	65 ± 9
1 wk	0.2 ± 0.4	−1.2 ± 0.5†	−0.25 ± 0.17	−0.16 ± 0.10	−10 ± 10	−37 ± 12
NIDDM obese						
Basal	88.3 ± 2.6	88.2 ± 2.6	9.4 ± 1.1	8.0 ± 0.8‡	183 ± 21	144 ± 22
1 wk	0.0 ± 0.3	−0.4 ± 0.3	0.01 ± 0.35	−1.27 ± 0.36§	−23 ± 34	−38 ± 24

Values are means ± SE. NIDDM, non-insulin-dependent diabetes mellitus. $n = 10$ for both groups.
*$P < 0.05$, †$P < 0.02$, ‡$P < 0.01$, §$P < 0.10$, vs. placebo with Student's *t* test.

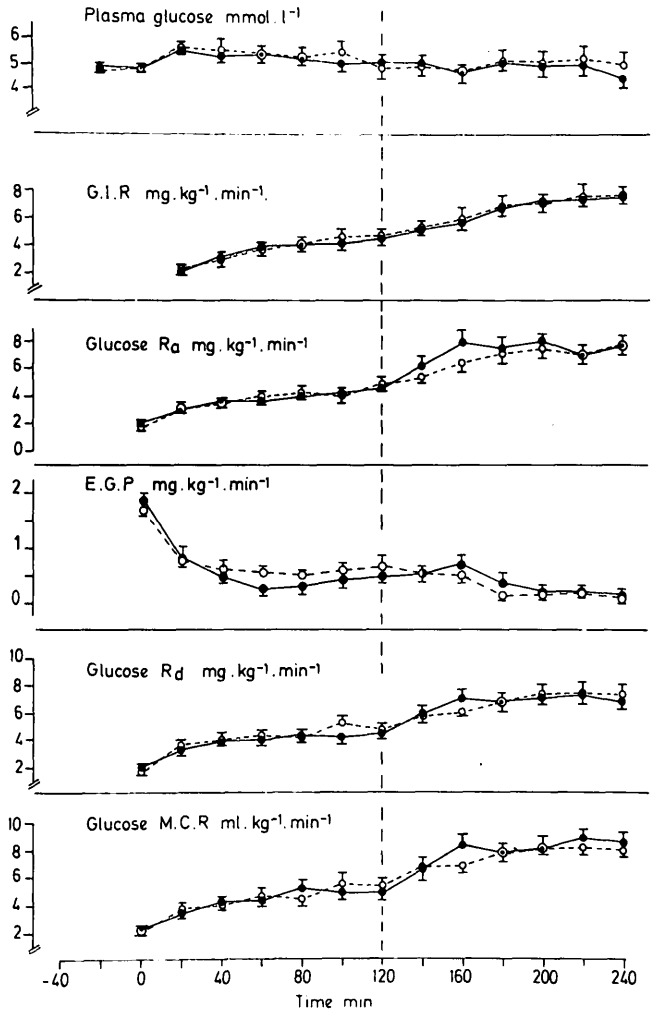

FIG. 1. Comparison of effects of *d*-fenfluramine (○) and placebo (●) on various parameters of glucose metabolism during euglycemic-hyperinsulinemic glucose clamp (insulin infusion rate 0.05 U · kg^{-1} · h^{-1} from 0 to 120 min and 0.10 U · kg^{-1} · h^{-1} from 120 to 240 min) in 10 obese nondiabetic subjects. Values are means ± SE. GIR, glucose infusion rate; R_a, rate of appearance; EGP, endogenous glucose production; R_d, rate of disappearance; MCR, metabolic clearance rate.

tween placebo and *d*-fenfluramine. Basal plasma FFA (780 ± 91 vs. 900 ± 202 μM, NS) and glycerol (167 ± 34 vs. 243 ± 85 μM, NS) levels tended to be slightly lower after *d*-fenfluramine. During the clamp, both FFA and glycerol concentrations decreased progressively and similarly in the two tests. Finally, MCR of insulin was slightly but not significantly higher after *d*-fenfluramine than after placebo (14.3 ± 0.6 vs. 13.0 ± 0.7 ml · kg^{-1} · min^{-1}, $P < 0.10$, and 14.1 ± 1.1 vs. 13.0 ± 0.8 ml · kg^{-1} · min^{-1}, NS, respectively) during the two consecutive insulin infusion rates. Thus, in the nondiabetic obese patients, a 1-wk treatment with *d*-fenfluramine did not induce significant changes in the hormonal and metabolic pattern or in the various parameters of glucose kinetics despite a slight but significant 1.2-kg weight reduction.

The diabetic obese patients showed only a discrete and not significant decrease in body weight after the 1-wk treatment with *d*-fenfluramine, so that the body weight was similar before the clamp, after placebo, and after the anorectic drug (Table 2). Fasting blood glucose levels were significantly lower after *d*-fenfluramine than after placebo, whereas plasma insulin concentrations tended to be slightly reduced (Table 2). Similarly, basal plasma C-peptide concentrations were not significantly lower after *d*-fenfluramine than after placebo (0.80 ± 0.10 vs. 0.83 ± 0.07 nM, respectively, NS). Note that the individuals with the most marked basal hyperglycemia had the greatest fall in fasting blood glucose levels during *d*-fenfluramine treatment ($r = 0.69$, $P < 0.05$).

Glucose kinetics data during the three insulin infusion rates of the glucose clamp are illustrated in Fig. 3. As mentioned, insulin was infused before the clamp in five patients to lower their plasma glucose levels to ~7 mM; consequently, glucose R_a, R_d, and MCR were not sig-

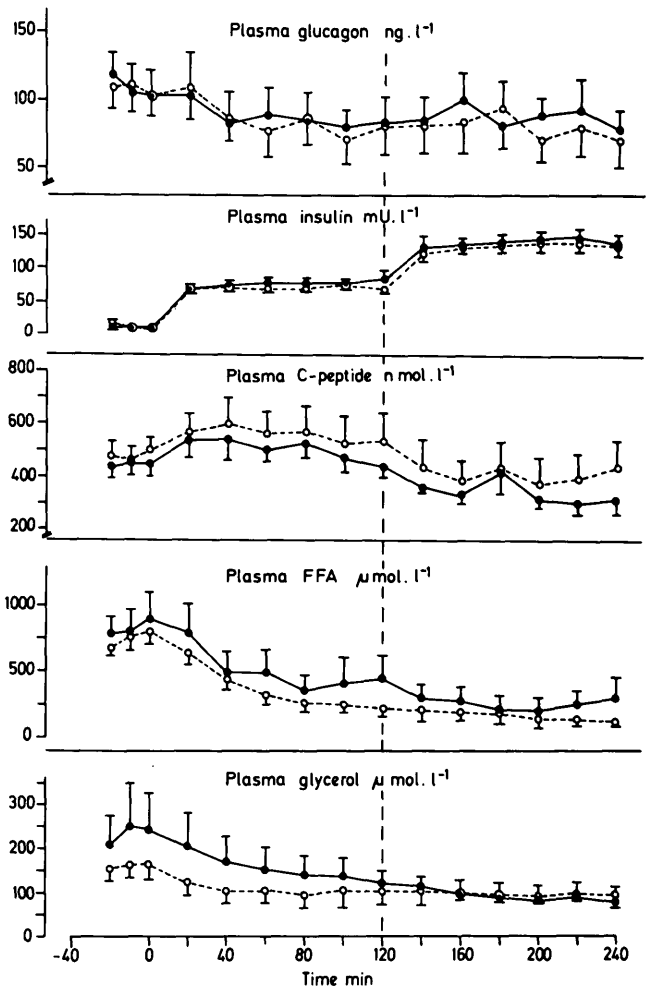

FIG. 2. Comparison of effects of *d*-fenfluramine (○) and placebo (●) on plasma glucagon, insulin, C-peptide, free fatty acid (FFA), and glycerol levels during euglycemic-hyperinsulinemic glucose clamp (insulin infusion rate 0.05 U · kg^{-1} · h^{-1} from 0 to 120 min and 0.10 U · kg^{-1} · h^{-1} from 120 to 240 min) in 10 obese nondiabetic subjects.

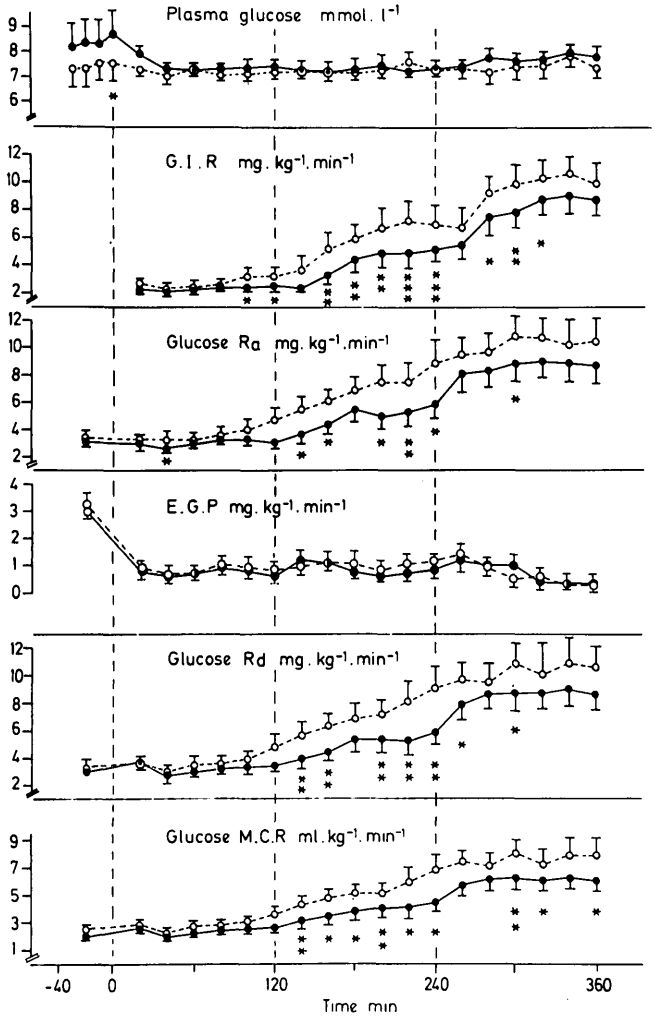

FIG. 3. Comparison of effects of *d*-fenfluramine (○) and placebo (●) on various parameters of glucose metabolism during euglycemic-hyperinsulinemic glucose clamp (insulin infusion rate 0.05 U · kg^{-1} · h^{-1} from 0 to 120 min, 0.10 U · kg^{-1} · h^{-1} from 120 to 240 min, and 0.50 U · kg^{-1} · h^{-1} from 240 to 360 min) in 10 obese non-insulin-dependent diabetic patients. Values are means ± SE. GIR, glucose infusion rate; R_a, rate of appearance; EGP, endogenous glucose production; R_d, rate of disappearance; MCR, metabolic clearance rate. *$P < 0.05$, **$P < 0.025$, ***$P < 0.005$, with Student's *t* test.

nificantly different between *d*-fenfluramine and placebo at time 0 before starting the clamp despite significant differences in fasting blood glucose levels. Plasma glucose levels were clamped at ~7.5 mM with a mean coefficient of variation of 4 ± 1% in both experimental conditions. To maintain steady plasma glucose levels, despite progressively increasing insulin infusion rates, GIR rose throughout the whole period of the test; note that the GIR values attained during the three insulin infusion rates were higher after *d*-fenfluramine than after placebo ($F = 3.1$, $P = 0.062$ from 0 to 120 min; $F = 12.8$, $P = 0.002$ from 120 to 240 min; and $F = 4.9$, $P = 0.034$ from 240 to 360 min with Zerbe's method [26]). Similarly, R_a, R_d, and MCR of glucose reached higher values after *d*-fenfluramine than after placebo. For instance, comparison of the glucose MCR data between both experimental conditions with Zerbe's method (26) gives the following results: $F = 1.80$, $P = 0.193$ from 0 to 120 min; $F = 7.03$, $P = 0.008$ from 120 to 240 min; and $F = 5.88$, $P = 0.022$ from 240 to 360 min. Glucose EGP was similarly suppressed in both experimental conditions.

Improvement of insulin-induced glucose disposal after *d*-fenfluramine was observed in the five patients who did not receive insulin before the clamp and in the five patients who did; it was of similar amplitude in both subgroups: 1.35 ± 0.36 vs. 1.36 ± 0.48 mg · kg^{-1} · min^{-1} (NS) for GIR, 1.61 ± 0.49 vs. 1.68 ± 0.78 mg · kg^{-1} · min^{-1} (NS) for R_d, and 1.20 ± 0.39 vs. 1.37 ± 0.51 ml · kg^{-1} · min^{-1} (NS) for MCR of glucose, considering the mean value of the last hour of the three insulin delivery rates in each subject. No significant correlation was observed between the increase in MCR of glucose recorded after *d*-fenfluramine and the fasting blood glucose levels measured before treatment ($r = -0.21$, NS).

Changes in plasma insulin, C-peptide, FFA, and glycerol concentrations are depicted in Fig. 4. The plateaus of insulinemia were not significantly different after *d*-fenfluramine and after placebo at the three consecutive insulin infusion rates. Plasma C-peptide levels slightly and progressively decreased throughout the test, and no significant differences were observed between the two experimental conditions. Initial plasma FFA (1150 ± 227 vs. 1640 ± 184 μM, $P < 0.05$) and glycerol (313 ± 78 vs. 436 ± 56 μM, NS) concentrations tended to be lower after *d*-fenfluramine than after placebo; both substrates decreased throughout the whole experiment in each experimental condition. However, plasma FFA levels tended to remain lower after *d*-fenfluramine than after placebo. Values of insulin MCR were similar in both experimental conditions: 13.1 ± 1.6 vs. 14.0 ± 2.1, 12.7 ± 1.3 vs. 12.7 ± 1.1, and 12.0 ± 0.4 vs. 11.2 ± 0.6 ml · kg^{-1} · min^{-1} during the three consecutive insulin infusion rates and after *d*-fenfluramine and placebo, respectively (NS).

Changes from 0 to 360 min in plasma glucagon, cortisol, and β-endorphin levels were not significantly different between *d*-fenfluramine and placebo. Plasma glucagon levels progressively decreased ($P < 0.05$) from 222 ± 71 to 95 ± 28 ng × L^{-1} and from 203 ± 74 to 109 ± 31 ng × L^{-1}; plasma cortisol concentrations slightly increased ($P < 0.05$) from 96 ± 20 to 160 ± 23 μg × L^{-1} and from 94 ± 15 to 156 ± 36 μg × L^{-1}; and plasma β-endorphin levels remained almost stable (NS), varying from 152 ± 15 to 166 ± 16 ng × L^{-1} and from 145 ± 18 to 161 ± 12 ng × L^{-1}.

Figure 5 illustrates the dose-response curve of glucose MCR in relation to plasma insulin levels in the two groups of obese patients both after placebo and *d*-fenfluramine. As expected, the dose-response curve of the diabetic patients was shifted to the right compared with that of the nondiabetic obese subjects. *d*-Fenfluramine did not significantly modify the curve of the obese subjects with

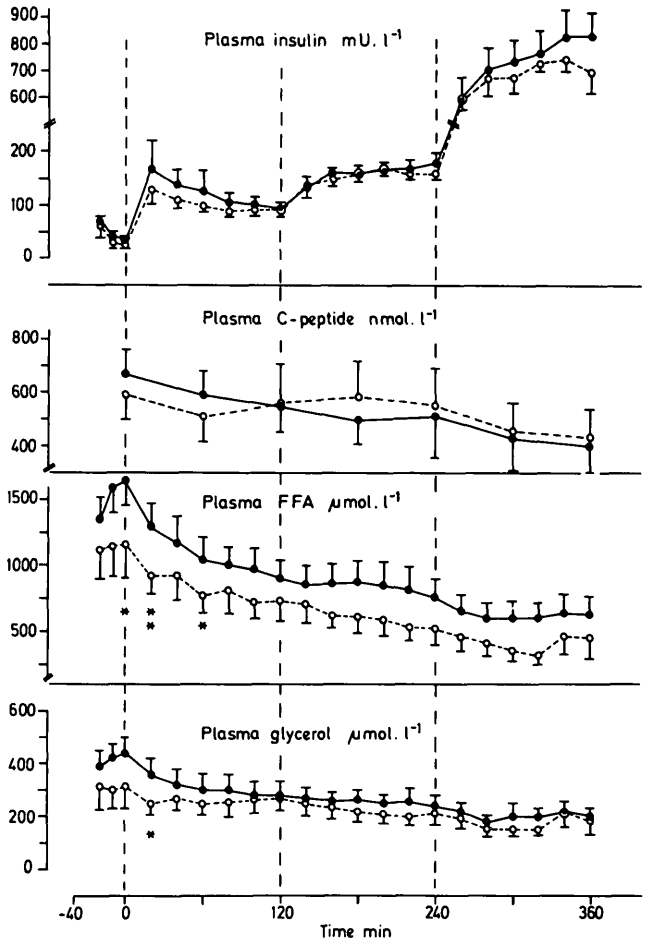

FIG. 4. Comparison of effects of *d*-fenfluramine (○) and placebo (●) on plasma insulin, C-peptide, free fatty acid (FFA), and glycerol levels during euglycemic-hyperinsulinemic glucose clamp (insulin infusion rate 0.05 U · kg^{-1} · h^{-1} from 0 to 120 min, 0.10 U · kg^{-1} · h^{-1} from 120 to 240 min, and 0.50 U · kg^{-1} · h^{-1} from 240 to 360 min) in 10 obese non-insulin-dependent diabetic patients. Values are means ± SE. *$P < 0.05$, **$P < 0.025$, with Student's *t* test.

normal oral glucose tolerance; in contrast, in the NIDDM obese patients, a moderate shift of the curve to the left and a significant ($P < 0.05$) increase of the glucose MCR values measured at the highest plasma insulin level were observed after *d*-fenfluramine.

The following side effects were recorded during treatment with *d*-fenfluramine: cold extremities ($n = 2$), dizziness ($n = 2$), dry mouth ($n = 2$), nausea ($n = 1$), and diarrhea ($n = 1$). In contrast, only one patient complained of nausea during the placebo period. All side effects were mild and spontaneously reversible.

CONCLUSIONS

Our results demonstrate that, in diabetic obese subjects, a 1-wk treatment with *d*-fenfluramine improved insulin sensitivity and induced better glycemic control independent of significant weight loss. These effects were not observed in obese subjects with normal oral glucose tolerance and normal fasting plasma insulin levels. However, the primary event remains hypothetical. Either *d*-fenfluramine directly improves insulin sensitivity, an effect that results in better glycemic control, or *d*-fenfluramine improves diet compliance and glycemic control, an effect that results in enhanced insulin action (27). Indeed, it could be argued that the rather short duration of the study, which was chosen to avoid bodyweight changes, did not preclude that diet remained unchanged in our ambulatory patients despite dietary advices and stable body weight. Nevertheless, the following points argue against the second hypothesis. First, the positive effect on glucose MCR was not observed at all in the nondiabetic obese patients, who showed a significant 1.2-kg weight loss during the 1-wk treatment with *d*-fenfluramine. Second, basal plasma insulin and C-peptide levels were not significantly reduced, as would be expected if diet were better respected. Finally, plasma FFA and glycerol levels were lower after *d*-fenfluramine, whereas lipolysis is increased in a classic fashion when calorie restriction occurs. Consequently, these findings support the hypothesis that the observed effect on glucose MCR in the diabetic patients does not result from the anorectic property of the drug and suggest that it is due to an independent specific action of the compound.

This interpretation is reinforced by various data available in the literature. Beside numerous animal studies (2), several investigations performed in humans, either

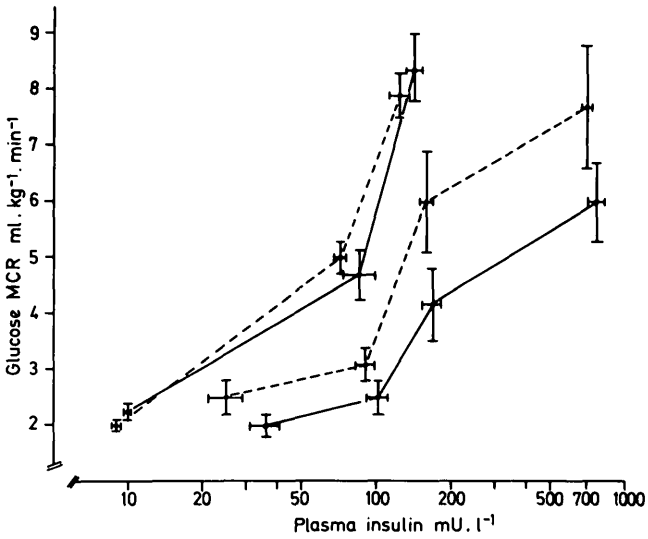

FIG. 5. Comparison of effects of *d*-fenfluramine (*dashed line*) and placebo (*solid line*) on dose-response curve of effect of increasing plasma insulin levels on glucose metabolic clearance rate (MCR). Two curves on *left* correspond with those of 10 obese nondiabetic subjects (nonsignificant effect of *d*-fenfluramine), whereas 2 curves on *right* correspond with those of 10 obese non-insulin-dependent diabetic patients (significant improvement after *d*-fenfluramine, $P < 0.05$). Values are means ± SE.

open (3,5) or double blind (4,6), give indirect evidence that fenfluramine improves insulin sensitivity in NIDDM patients; indeed, fasting blood glucose levels and blood glucose excursions after a meal or during an oral glucose tolerance test were reduced despite similar or even lower plasma insulin levels. In addition, a few carefully performed studies in humans with a forearm perfusion method have demonstrated that fenfluramine potentiates muscle glucose uptake (3,28). A previous study confirms a significant improvement of the overall glucose uptake during a euglycemic-hyperinsulinemic glucose clamp in obese NIDDM patients treated with 60 mg fenfluramine/day for 4 wk (7). Despite this rather long treatment period, body weight remained unchanged in those patients, but nevertheless, fasting blood glucose levels fell remarkably by ~5 mM. Contrasting with the positive results observed in the diabetic patients, no significant effects were recorded in healthy volunteers after 3 days of fenfluramine (60 mg/day) during a frequently sampled intravenous glucose tolerance test with analysis by the minimal-model method (7).

We confirmed these results with *d*-fenfluramine, the active moiety of the racemic mixture (9), with a significant effect on the insulin-induced glucose disposal only in diabetic patients. In contrast to data reported in the rat (8), we were not able to demonstrate any significant effect of *d*-fenfluramine on the hepatic glucose production. However, in our study and in contrast to the effect observed in fat-fed rats (8), EGP was already almost completely abolished in the glucose clamp performed under placebo, so that it was impossible to detect any additional effect at this level. It has been hypothesized that *d*-fenfluramine improves insulin action by reducing noradrenergic neural drive to hepatic glucose output (8). We did not measure catecholamines in our study, but other counterregulatory hormones, e.g., glucagon, cortisol, and β-endorphin, were not significantly altered by *d*-fenfluramine.

In the only study with euglycemic-hyperinsulinemic glucose clamps in humans, fenfluramine was shown to increase insulin clearance (7). Because previous studies have demonstrated reduced insulin clearance in insulin-resistant states (29), Pestell et al. (7) considered the increased insulin clearance during fenfluramine therapy to be consistent with increased insulin sensitivity, possibly through increased insulin-receptor binding. Although we observed a slight tendency toward increased MCR of insulin after *d*-fenfluramine in the nondiabetic obese group, the effect was not observed in the diabetic obese patients, who were precisely those exhibiting an increased insulin sensitivity after treatment. Moreover, the dose-response curve suggested that the effect predominates at the postbinding rather than the binding step of insulin to its receptor.

One striking finding of our study was the decrease in basal FFA plasma levels after *d*-fenfluramine; this effect tended to be already present, although not significantly, in the nondiabetic obese subjects, and became significant and more marked in the diabetic obese patients who had particularly high plasma FFA levels in the placebo conditions. Our protocol did not allow for determination of whether this effect either represents a primary action of the drug or is only secondary to the improved glucose metabolism. Nevertheless, in agreement with Randle's cycle concept (30), which has been exemplified in obesity and NIDDM (24,31,32), we hypothesized that the lower FFA plasma levels observed after *d*-fenfluramine may be at least partially responsible for the better insulin action on glucose disposal. Such an indirect mechanism would be consistent with in vitro studies showing the failure of fenfluramine to affect basal and insulin-stimulated hexose transport in rat skeletal muscle (33).

In conclusion, our results demonstrate significantly reduced fasting blood glucose levels, improved insulin-induced glucose disposal, and lower plasma FFA levels after a 1-wk treatment with *d*-fenfluramine in obese NIDDM patients independent of any significant weight loss. Better insulin action seems to be located at the peripheral level and to predominate at a post–insulin-receptor binding step. Whatever the intimate mechanism(s) involved, it is important to keep in mind that these findings were observed after only a 1-wk treatment period. Thus, it is mandatory to confirm such improvement of insulin sensitivity during long-term studies before considering *d*-fenfluramine as an adjunct therapy in obese patients remaining hyperglycemic despite diet prescription.

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