Bromocriptine

A novel approach to the treatment of type 2 diabetes

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OBJECTIVE — In vertebrates, body fat stores and insulin action are controlled by the temporal interaction of circadian neuroendocrine oscillations. Bromocriptine modulates neurotransmitter action in the brain and has been shown to improve glucose tolerance and insulin resistance in animal models of obesity and diabetes. We studied the effect of a quick-release bromocriptine formulation on glucose homeostasis and insulin sensitivity in obese type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS — There were 22 obese subjects with type 2 diabetes randomized to receive a quick-release formulation of bromocriptine (n = 15) or placebo (n = 7) in a 16-week double-blind study. Subjects were prescribed a weight-maintaining diet to exclude any effect of changes in body weight on the primary outcome measurements. Fasting plasma glucose concentration and HbA_{1c} were measured at 2- to 4-week intervals during treatment. Body composition (underwater weighing), body fat distribution (magnetic resonance imaging), oral glucose tolerance (oral glucose tolerance test [OGTT]), insulin-mediated glucose disposal, and endogenous glucose production (2-step euglycemic insulin clamp, 40 and 160 mU $\cdot$ min^{-1} $\cdot$ m^{-2}) were measured before and after treatment.

RESULTS — No changes in body weight or body composition occurred during the study in either placebo- or bromocriptine-treated subjects. Bromocriptine significantly reduced HbA_{1c} (from 8.7 to 8.1%, P = 0.009) and fasting plasma glucose (from 190 to 172 mg/dl, P = 0.02) levels, whereas these variables increased during placebo treatment (from 8.5 to 9.1%, NS, and from 187 to 223 mg/dl, P = 0.02, respectively). The differences in HbA_{1c} (Δ = 1.2%, P = 0.01) and fasting glucose (Δ = 54 mg/dl, $P < 0.001$) levels between the bromocriptine and placebo group at 16 weeks were highly significant. The mean plasma glucose concentration during OGTT was significantly reduced by bromocriptine (from 294 to 272 mg/dl, P = 0.005), whereas it increased in the placebo group. No change in glucose disposal occurred during the first step of the insulin clamp in either the bromocriptine- or placebo-treated group. During the second insulin clamp step, bromocriptine improved total glucose disposal from 6.8 to 8.4 mg $\cdot$ min^{-1} $\cdot$ kg^{-1} fat-free mass (FFM) (P = 0.01) and nonoxidative glucose disposal from 3.3 to 4.3 mg $\cdot$ min^{-1} $\cdot$ kg^{-1} FFM ($P < 0.05$), whereas both of these variables deteriorated significantly ($P \leq 0.02$) in the placebo group.

CONCLUSIONS — Bromocriptine improves glycemic control and glucose tolerance in obese type 2 diabetic patients. Both reductions in fasting and postprandial plasma glucose levels appear to contribute to the improvement in glucose tolerance. The bromocriptine-induced improvement in glycemic control is associated with enhanced maximally stimulated insulin-mediated glucose disposal.

Diabetes Care 23:1154–1161, 2000

Type 2 diabetes is characterized by elevated fasting and postprandial plasma glucose concentrations, which result from increased endogenous glucose production (EGP), decreased insulin-mediated muscle glucose disposal and suppression of endogenous glucose release, and inadequate pancreatic insulin secretion (1). Obesity is a well-established risk factor for type 2 diabetes (2). Impaired suppression of EGP and reduced insulin-mediated glucose disposal are dominant metabolic features of the obese state (3), and it has been estimated that 60–80% of type 2 diabetic patients are obese (4). It has been hypothesized that the development of obesity and its accompanying insulin resistance may have been an adaptation that improved survival in times of famine, i.e., the thrifty gene hypothesis (5). It is well established that many vertebrate species develop obesity and insulin resistance in preparation for hibernation or during winter periods (6). Extensive experimental evidence indicates that circadian neuroendocrine rhythms play a pivotal role in the development of seasonal changes in body fat stores and insulin sensitivity (7). Specifically, temporal changes in the interaction of 2 distinct neural circadian oscillations, mediated by dopaminergic and serotonergic neurotransmitter activity, have been shown to regulate the dramatic seasonal alterations in body weight and body composition that are characteristic of all vertebrate classes from teleosts to mammals (7). Data obtained in rats, pigs, and humans suggest that similar mechanisms may play a role in the development of nonseasonal obesity and insulin resistance (7–9).

Bromocriptine mesylate, an ergot derivative, is a sympatholytic dopamine D_2 receptor agonist that exerts inhibitory effects on serotonin turnover in the central nervous system (10). It has been proposed that bromocriptine can reverse many of the metabolic alterations associated with obesity by resetting central (hypothalamic) circadian organization of monoamine neuronal activi-

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Received for publication 12 November 1999 and accepted in revised form 27 April 2000.

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Abbreviations: CV, coefficient of variation; EGP, endogenous glucose production; FFA, free fatty acid; FFM, fat-free mass; FPG, fasting plasma glucose; GIR, exogenous glucose infusion rate; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; R_a, rate of endogenous glucose appearance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ties. Indeed, bromocriptine, if administered systemically (9,11–13) or into the cerebral ventricle (14) during the early hours of the light cycle, prevents or reverses seasonal fattening, insulin resistance, and decreased endogenous (hepatic) glucose production in mammals. Moreover, timed bromocriptine treatment decreased body weight and improved glucose tolerance in obese individuals who were instructed to follow a hypocaloric diet (15). Bromocriptine has also been shown to reduce mean daylong plasma glucose, triglyceride, and free fatty acid (FFA) levels in the absence of a change in body weight in obese nondiabetic women (16). Finally, in an open-label study, bromocriptine reduced body fat stores, improved glycemic control, and diminished the need for oral hypoglycemic agents in obese patients with type 2 diabetes (17).

In the present study, we examined the effects of a quick-release bromocriptine preparation on glycemic control, insulin-mediated glucose disposal, EGP, and body composition in obese type 2 diabetic patients. To exclude any impact of changes in body weight on these parameters, subjects were prescribed a weight-maintaining diet.

RESEARCH DESIGN AND METHODS

Subjects

There were 22 obese type 2 diabetic patients recruited from the outpatient clinic of the Texas Diabetes Institute. Entry criteria included a fasting plasma glucose concentration between 140 and 240 mg/dl, stable body weight for at least 3 months before inclusion, and a BMI between 28 and 42 kg/m^2 for women or 27 and 42 kg/m^2 for men. All patients were in good general health without evidence of cardiac, hepatic, renal, or other chronic diseases, as determined by history, examination, and screening blood tests. Patients taking insulin or drugs known to affect insulin sensitivity (including metformin or troglitazone) were not eligible. Subjects who were taking sulfonylurea drugs were eligible if the medication dose was stable for at least 3 months before the study. In no subject was the sulfonylurea dose changed after his or her recruitment into the study. Other patient characteristics are shown in Table 1. All subjects gave signed voluntary informed consent before participation. The protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

Study design

The study had a double-blind placebo-controlled parallel design with 2:1 (bromocriptine:placebo) randomization. The treatment period was 16 weeks. All subjects were prescribed a weight-maintaining diet according to the guidelines of the American Diabetes Association (18). Participants maintained dietary logs and met with the dietitian every 2 weeks throughout the study to ensure compliance with the diet. During the 2 weeks before the start of treatment, subjects received the following: *1*) oral glucose tolerance test (OGTT), *2*) measurement of insulin sensitivity with the euglycemic insulin clamp technique, *3*) determination of body composition by underwater weighing, *4*) quantitation of visceral and subcutaneous fat depots by magnetic resonance imaging (MRI), and *5*) 24-h measurement of blood pressure. Studies were carried out at 8:00 A.M. after a 10- to 12-h overnight fast. All measurements were repeated after 16 weeks of treatment with bromocriptine or placebo. There was no significant change in body weight in any subject during the entire study period. Therefore, it was not necessary for the dietitian to implement any change in dietary intake in any subject.

Fasting plasma glucose, HbA_{1c}, and OGTT. Fasting plasma glucose (FPG) concentration and HbA_{1c} were measured at −2 and 0 weeks before and every 4 weeks after the start of treatment with bromocriptine or placebo. During the OGTT, baseline blood samples for determination of plasma glucose, FFA, insulin, and C-peptide concentrations were drawn at −15 and 0 min. At $t = 0$, each subject ingested 75 g glucose dissolved in 300 ml flavored water, and blood samples for plasma glucose, FFA, insulin, and C-peptide were obtained at 15-min intervals for 2 h.

Euglycemic insulin clamp. Subjects received a 2-step euglycemic insulin clamp to examine the effect of bromocriptine and placebo on the suppression of EGP and insulin-stimulated glucose uptake by peripheral tissues. A primed (25 μCi × FPG/100) continuous (0.25 μCi/min) infusion of [3-^{3}H]glucose was started at time −180 min via a catheter placed into an antecubital vein and continued throughout the study. No tritiated glucose was added to the exogenously infused cold glucose because at the low rates of insulin-mediated glucose disposal observed in diabetic subjects in the present study, we previously have shown that the tracer method provides a valid measurement of glucose turnover (19). At $t = 0$, a primed continuous infusion of human regular insulin (Novolin; Novo Nordisk, Princeton, NJ) was started at a rate of 40 mU · min^{-1} · m^{-2} body surface area and continued for 90 min as previously described (20). At $t = 90$ min, the insulin space was reprimed and the insulin infusion rate was increased to 160 mU · min^{-1} · m^{-2} for another 90 min. The plasma glucose concentration was allowed to drop spontaneously until it reached ~90 mg/dl (5 mmol/l), at which level it was clamped by adjusting a variable infusion of 20% dextrose (20). Because of the severity of the insulin resistance, the desired euglycemic plateau was not achieved during the first insulin clamp step in many diabetic subjects.

Arterialized venous blood was collected from a catheter that was inserted retrogradely into a vein on the dorsum of the hand, which was then placed in a heated box (60°C). Baseline blood samples for determination of plasma [3-^{3}H]glucose radioactivity and plasma glucose and insulin concentrations were obtained at −30, −20, −10, −5, and 0 min. Throughout the insulin clamp, blood samples for determination of plasma glucose were drawn every 5 min. During the insulin clamp, blood samples for determination of plasma insulin concentration and [3-^{3}H]glucose specific activity were collected every 10–15 min. Rates of oxygen consumption and carbon dioxide production were measured by continuous indirect calorimetry using a ventilated hood system (DeltaTrac II; SensorMedics, Yorba Linda, CA) during the last 40 min of the basal state and each insulin infusion step.

Underwater weighing. Body composition was measured by underwater weighing using the Submerged Weight Electronic Evaluation Tank System (Ergo Science, Charlestown, MA). Briefly, subjects were instructed to sit on an electronic weighing scale (chair) in an empty open tank and body weight was measured. Subjects were asked to maximally exhale in a spirometer to determine forced vital capacity for estimation of residual lung volume. Subsequently, the tank was filled with water and the subject was asked to maximally exhale and submerge his or her head for measurement of underwater body weight. Five underwater weighing measurements were obtained and the mean was determined. All acquired data were electronically stored and transmitted to a central database for calculation of body volume and density.

Table 1—*Subject characteristics*

	Bromocriptine	Placebo
n	15	7
M:F	6:9	2:5
Sulfonylureas:diet	8:7	6:1
Age (years)	56 ± 2	50 ± 3
Diabetes duration (years)	3.2 ± 0.6	3.5 ± 0.8
Weight (kg)	89.6 ± 2.8	93.4 ± 5.7
BMI (kg/m^2)	33.7 ± 0.9	35.7 ± 1.3
FPG (mg/dl)	190 ± 13	187 ± 22
Fasting plasma insulin (μU/ml)	21 ± 2	23 ± 4
HbA_{1c} (%)	8.7 ± 0.4	8.5 ± 0.5
Body fat (%)	47 ± 2	54 ± 2
Fat mass (kg)	42 ± 8	48 ± 9
FFM (kg)	48 ± 2	46 ± 4
Abdominal subcutaneous fat area (cm^2)	459 ± 33	471 ± 55
Visceral fat area (cm^2)	204 ± 14	146 ± 16
Total cholesterol (mg/dl)	190 ± 7	202 ± 10
LDL cholesterol (mg/dl)	117 ± 6	123 ± 10
HDL cholesterol (mg/dl)	42 ± 2	43 ± 3
Triglycerides (mg/dl)	157 ± 15	180 ± 14
FFA (mEq/l)	0.79 ± 0.07	0.78 ± 0.07

Data are *n* or means ± SD. To convert values for glucose to millimoles per liter, multiply by 0.056. To convert values for insulin to picomoles per liter, multiply by 6. To convert values for cholesterol to millimoles per liter, multiply by 0.026. To convert values for triglycerides to millimoles per liter, multiply by 0.011.

When fat mass was determined in the same subject on the same day on 10 consecutive measurements, the coefficient of variation (CV) was <1%. The CV in the same subject whose fat mass was determined on 5 consecutive days was also <1%.

Body fat distribution. Visceral and subcutaneous fat depots were measured by MRI, using imaging and processing procedures that have been published previously (21). Briefly, images were acquired on a 1.9 T Elscint Prestige MRI system, using a T1-weighted spin echo pulse sequence with a TR of 500 ms and a TE of <20 s. A sagittal localizing image was used to center transverse sections on the line through the umbilicus and the space between L4 and L5. Ten 5.0-mm–thick sections were acquired with a gap of 1.0 mm to prevent signal crossover from adjacent sections. The field of view ranged from 30 to 50 cm, depending on body size, to ensure 5.0-mm pixel spacing. Phase encoding was in the anteroposterior direction to minimize the effects of motion-induced phase artifacts, and signals were averaged to further reduce effects of motion-related artifacts. Additionally, respiratory gating was used to combat motion-induced artifacts and to reduce the blurring of fat boundaries in the anterior region of the abdomen. Images were processed using Alice software (Perceptive Systems, Boulder, CO) to determine abdominal subcutaneous and visceral fat areas. The CV in visceral and subcutaneous fat area in the same subject studied on 24 separate days was <1% (21).

Blood pressure monitoring. There were 24-h blood pressure recordings obtained using an Ambulatory Blood Pressure Monitor 90207 (Space Labs Medical, Redmond, WA).

Drug treatment. After completion of the above studies, subjects were instructed to take 1 tablet of the study drug (0.8 mg bromocriptine or placebo) daily for the first week. The daily dosage was increased by 1 tablet every week. All subjects tolerated the dose-escalation protocol without significant side effects, and the targeted dosage of 6 tablets of bromocriptine (4.8 mg) per day was achieved after 6 weeks. The study medication was ingested between 7:30 and 8:30 A.M.

Assays

Plasma glucose concentration was measured using the glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA). HbA_{1c} was determined by a latex immunoagglutination inhibition method on a DCA 2000 Analyzer (Bayer, Elkhart, IN). The inter- and intra-assay CVs were 2.2 and 2.4%, respectively. Plasma insulin concentration was measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA) with an intra-assay CV <5% and an interassay CV <7% at insulin levels >15 μU/ml. Plasma C-peptide was measured by radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX) with intra- and interassay CVs <10% at C-peptide levels <10 ng/ml. Plasma FFA concentrations were measured by a colorimetric method (Wako Chemicals, Neuss, Germany) with an intraassay CV of <3% at FFA levels <1 mmol/l. Tritiated glucose specific activity was determined in deproteinized plasma samples as described previously (22).

Calculations

Under steady-state postabsorptive conditions, the rate of endogenous glucose appearance (R_a) is calculated as the [3-^{3}H]glucose infusion rate (dpm/min) divided by the steady-state plasma [3-^{3}H]glucose specific activity (dpm/mg). During the insulin clamp, nonsteady conditions prevail and R_a was calculated from the equation by Steele (23) using 0.65 as the pool fraction (24). EGP (mg/min) was calculated as follows: EGP = R_a – GIR, where GIR equals exogenous glucose infusion rate (mg/min). Total glucose disposal equals the sum of residual EGP plus GIR. Rates of glucose and lipid oxidation were calculated from respiratory gas exchange measurements using formulae described previously (25). During the euglycemic insulin clamp, nonoxidative glucose disposal, which primarily represents glycogen synthesis (26), was calculated by subtracting the rate of glucose oxidation from the rate of total body glucose disposal.

Percent body fat was calculated from underwater weighing data using the formulas described by Brozek et al. (27). Residual lung volume (RV) (liters) was calculated as RV = 0.24 × FVC, where FVC equals forced vital capacity (liters).

The mean plasma glucose, insulin, and FFA concentrations during the OGTT were calculated by dividing the weighted values at each time point by the number of measurements.

Statistical analysis

Statistical analyses were performed with StatView for Windows, version 5.0 (SAS Institute, Cary, NC). Values before and after treatment within each group were compared

Table 2—*Summary of body weight and composition in diabetic patients before and after treatment with bromocriptine or placebo*

	Weight (kg)	BMI (kg/m^2)	Body fat (%)	Fat mass (kg)	Abdominal subcutaneous fat (cm^2)	Visceral fat (cm^2)
Bromocriptine						
Before	89.6 ± 2.8	33.7 ± 0.9	47 ± 2	42 ± 8	459 ± 33	204 ± 14*
After	90.0 ± 2.9	33.8 ± 0.9	46 ± 2	41.5 ± 6	437 ± 34	213 ± 13
Placebo						
Before	93.4 ± 5.7	35.7 ± 1.3	54 ± 2	48 ± 9	471 ± 55	146 ± 16
After	94.3 ± 5.3	36.0 ± 1.2	49 ± 3	46 ± 7	505 ± 37	166 ± 12

Data are means ± SD.*P = 0.03 for bromocritpine vs. placebo during the baseline measurement.

with the paired Student's t test. Between-group differences (placebo vs. bromocriptine) were analyzed using analysis of variance with repeated measures over time. Data are presented as means ± SEM.

RESULTS

Subject characteristics

At baseline, there were no significant differences in subject characteristics between the placebo and bromocriptine groups (Table 1). Bromocriptine treatment was well tolerated, with rhinitis and mild nausea reported as the most frequent adverse events (in 4 and 3 subjects, respectively). These side effects disappeared within 2 weeks after the start of therapy.

Body weight and composition

Neither bromocriptine nor placebo administration was associated with any significant changes from baseline in body weight (bromocriptine, 89.6 ± 2.8 vs. 90.0 ± 2.9 kg; placebo, 93.4 ± 5.7 vs. 94.3 ± 5.3 kg), fat mass, percentage fat mass, or abdominal fat distribution (Table 2).

Fasting plasma glucose and HbA_{1c} concentrations

At 16 weeks, the fasting plasma glucose concentration was reduced by bromocriptine treatment from 190 ± 13 to 172 ± 14 mg/dl (from 10.6 ± 0.7 to 9.5 ± 0.8 mmol/l [P = 0.02]), whereas it increased with placebo treatment from 187 ± 22 to 223 ± 26 mg/dl (from 10.5 ± 1.2 to 12.5 ± 1.5 mmol/l [P = 0.02]). HbA_{1c} was reduced in bromocriptine-treated patients from 8.7 ± 0.4 to 8.1 ± 0.5% (P = 0.009), whereas it increased in the placebo group from 8.5 ± 0.5 to 9.1 ± 0.6% (NS) (Fig. 1). The differences in FPG ($P < 0.001$) and HbA_{1c} (P = 0.01) between bromocriptine and placebo groups were highly significant (Fig. 2).

OGTT

During the OGTT, the mean plasma glucose concentration in the bromocriptine-treated group declined from 294 ± 14 to 272 ± 17 mg/dl (from 16.5 ± 0.8 to 15.2 ± 1.0 mmol/l [P = 0.005]), whereas the mean plasma glucose concentration rose in the placebo group from 289 ± 17 to 313 ± 28 mg/dl (16.2 ± 1.0 vs. 17.5 ± 1.6 mmol/l [NS]) (Fig. 1). The difference in mean plasma glucose concentration during the OGTT between the bromocriptine and placebo groups was significant (P = 0.02). Bromocriptine treatment did not affect the mean plasma insulin (65 ± 13 vs. 66 ± 10 μU/ml [390 ± 78 vs. 396 ± 60 pmol/l], NS), C-peptide (6.0 ± 0.7 vs. 5.2 ± 0.5 ng/ml [2.0 ± 0.2 vs. 1.7 ± 0.2 nmol/l], NS), or FFA (0.50 ± 0.04 vs. 0.54 ± 0.04 mEq/l, NS) concentrations during the OGTT. The mean plasma insulin (54 ± 15 vs. 47 ± 17 μU/ml [324 ± 90 vs. 282 ± 102 pmol/l], NS), C-peptide (6.4 ± 0.9 vs. 5.1 ± 1.0 ng/ml [2.1 ± 0.3 vs. 1.7 ± 0.3 nmol/l], NS), and FFA (0.60 ± 0.06 vs. 0.62 ± 0.07 mEq/l, NS) concentrations did not change during placebo treatment.

Euglycemic insulin clamp

Basal EGP was not changed by bromocriptine (3.3 ± 0.2 vs. 3.1 ± 0.2 mg · min^{-1} · kg^{-1} fat-free mass [FFM], NS) or by placebo (3.4 ± 0.4 vs. 3.2 ± 0.2 mg · min^{-1} · kg^{-1} FFM, NS) treatment.

During the first step of the insulin clamp performed before the start of treatment, the steady-state plasma insulin concentrations were similar in bromocriptine- and placebo-treated subjects (80 ± 4 vs. 83 ± 8 μU/ml [480 ± 24 vs. 458 ± 48 pmol/l], respectively). Similar plasma insulin concentrations were reached during the first step of the insulin clamp performed after 16 weeks of treatment in both groups (81 ± 5 vs. 81 ± 10 μU/ml [486 ± 30 vs. 486 ± 60 pmol/l], respectively). The mean plasma glucose concentrations (60- to 90-min time period) during the first step of the insulin clamp performed before and after bromocriptine (121 ± 12 vs. 108 ± 7 mg/dl

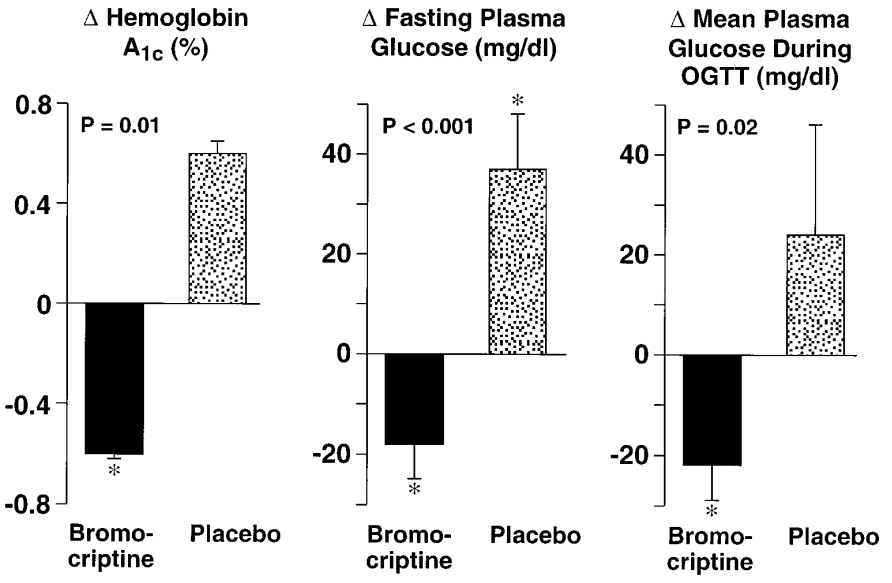

Figure 1—*Mean HbA_{1c}, FPG, and change in mean plasma glucose concentration during the OGTT in bromocriptine- and placebo-treated subjects.* P *values indicate the difference between bromocriptine- and placebo-treated groups. *Significant (*P *< 0.05) change from baseline within each group.*

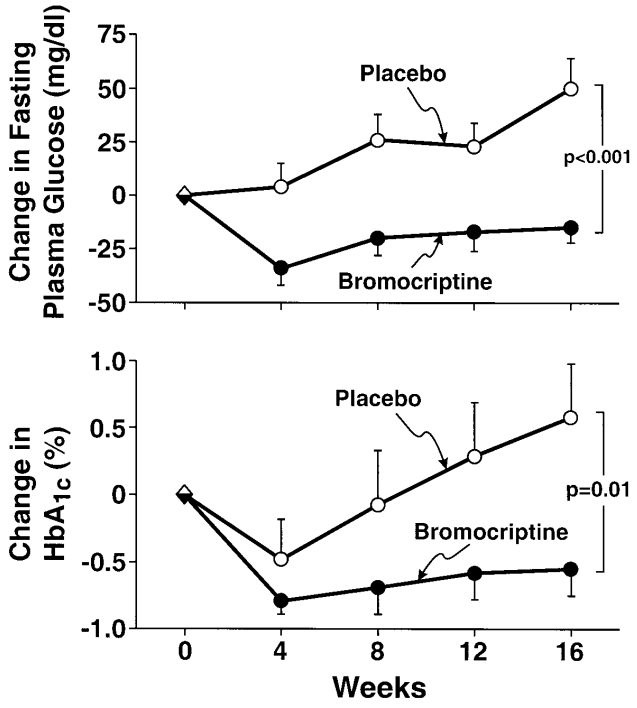

Figure 2—*Time course of change from baseline in HbA_{1c} and FPG concentrations in bromocriptine- and placebo-treated subjects.* P *values indicate differences between the 2 groups at 16 weeks.*

[6.8 ± 0.7 vs. 6.2 ± 0.6 mmol/l], NS) and placebo (111 ± 11 vs. 133 ± 13 mg/dl [6.6 ± 0.4 vs. 7.4 ± 0.7 mmol/l], NS) treatment also were similar in both groups. During the first step of the insulin clamp, neither bromocriptine (total glucose disposal, 3.7 ± 0.3 vs. 3.7 ± 0.3 mg · min^{-1} · kg^{-1} FFM, NS) nor placebo (total glucose disposal, 4.3 ± 0.5 vs. 3.4 ± 0.5 mg · min^{-1} · kg^{-1} FFM, NS) had any effect on total glucose disposal. Nonoxidative glucose disposal and glucose oxidation during the first step of the insulin clamp were similar in bromocriptine- and placebo-treated groups and were unaffected by either treatment. EGP was suppressed similarly by bromocriptine (1.2 ± 0.3 [before] vs. 1.2 ± 0.2 [after] mg · min^{-1} · kg^{-1} FFM, NS) and placebo (1.4 ± 0.2 [before] vs. 1.2 ± 0.3 [after] mg · min^{-1} · kg^{-1} FFM, NS).

The steady-state plasma insulin levels during the second step of the initial insulin clamp were similar in bromocriptine- and placebo-treated subjects (377 ± 20 vs. 347 ± 25 μU/ml [2,262 ± 120 vs. 2,082 ± 150 pmol/l], respectively). Similar steady-state plasma insulin concentrations were achieved after treatment in both groups (359 ± 15 vs. 357 ± 27 μU/ml [2,154 ± 90 vs. 2,142 ± 162 pmol/l], respectively). The steady-state plasma glucose concentration during the second step of the insulin clamp performed before treatment was similar in bromocriptine- and placebo-treated subjects (97 ± 4 vs. 90 ± 1 mg/dl [5.4 ± 0.2 vs. 5.0 ± 0.1 mmol/l], NS). Similar plasma glucose levels were maintained in the second step of the insulin clamp performed after 16 weeks of treatment (90 ± 1 vs. 91 ± 1 mg/dl [5.0 ± 0.1 vs. 5.1 ± 0.1 mmol/l], respectively, NS). The rate of total glucose disposal was increased by 24% in bromocriptine-treated subjects during the second insulin clamp step (from 6.8 ± 0.8 to 8.4 ± 0.6 mg · min^{-1} · kg^{-1} FFM, P = 0.01), whereas it decreased by 27% in the placebo-treated group (from 8.7 ± 1.0 to 6.4 ± 0.7 mg · min^{-1} · kg^{-1} FFM, P = 0.02) (Fig. 3). The difference between the 2 groups was highly significant (P = 0.001). The improvement in insulin sensitivity after bromocriptine treatment was entirely accounted for by a 32% increase in nonoxidative glucose disposal (from 3.3 ± 0.8 to 4.3 ± 0.5 mg · min^{-1} · kg^{-1} FFM, $P < 0.05$). Nonoxidative glucose disposal decreased by 52% in the placebo-treated group (from 4.6 ± 0.8 to 2.2 ± 0.7 mg · min^{-1} · kg^{-1} FFM, P = 0.01) (Fig. 3). This difference in nonoxidative glucose disposal between the 2 groups was highly significant ($P < 0.002$). Glucose oxidation was not affected by either treatment (bromocriptine, 3.8 ± 0.3 vs. 4.2 ± 0.3 mg · min^{-1} · kg^{-1} FFM, NS; placebo, 4.2 ± 0.5 vs. 4.3 ± 0.3 mg · min^{-1} · kg^{-1} FFM, NS). Suppression of EGP by insulin was similar in both groups before treatment and was not affected by bromocriptine (0.6 ± 0.1 vs. 0.8 ± 0.2 mg · min^{-1} · kg^{-1} FFM, NS) or placebo (0.7 ± 0.2 vs. 0.9 ± 0.2 mg · min^{-1} · kg^{-1} FFM, NS) treatment.

Plasma lipids

The total plasma cholesterol concentration decreased slightly, though not significantly, from baseline in bromocriptine-treated patients (from 190 ± 7 to 178 ± 6 mg/dl, P = 0.06) and remained unchanged in the

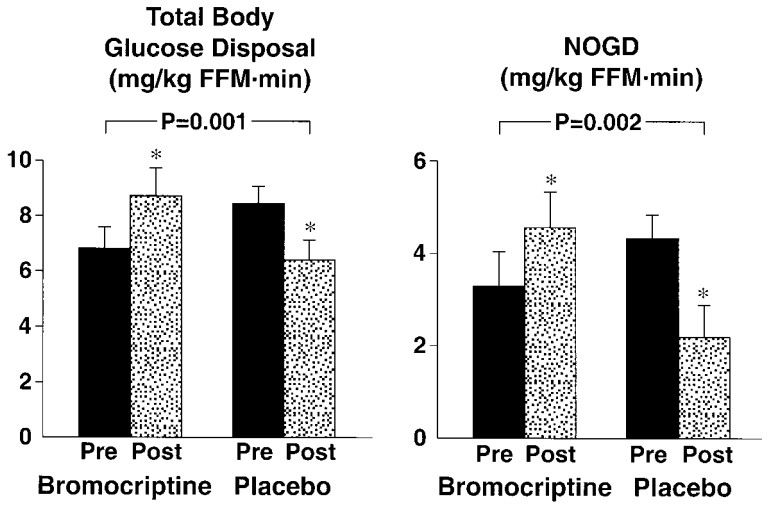

Figure 3—*Insulin-mediated total and nonoxidative glucose disposal (NOGD) during the second step of the euglycemic insulin clamp in bromocriptine- and placebo-treated type 2 diabetic subjects.* P *values indicate the difference between bromocriptine- and placebo-treated groups. *Significant (*P < 0.05*) change within each group.*

Table 3—*Plasma lipid levels (milligrams per deciliter) in diabetic patients before and after treatment with bromocriptine or placebo*

	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
Bromocriptine				
Before	190 ± 7	117 ± 6	42 ± 2	157 ± 15
After	176 ± 7	110 ± 7	38 ± 2	140 ± 17
Placebo				
Before	202 ± 10	123 ± 10	43 ± 3	180 ± 14
After	192 ± 13	117 ± 13	38 ± 3	186 ± 26

Data are means ± SD.

placebo-treated group. The difference between bromocriptine- and placebo-treated patients was not statistically significant. No significant changes in plasma LDL cholesterol, HDL cholesterol, or triglyceride concentrations were observed in either bromocriptine- or placebo-treated subjects (Table 3).

Blood pressure

The mean blood pressure and heart rate were similar during the day and night periods (8:00 A.M. to 8:00 P.M. and 8:00 P.M. to 8:00 A.M, respectively; data not shown). Mean 24-h blood pressure was not changed by either bromocriptine (95 ± 3 vs. 95 ± 3 mmHg, NS) or placebo (91 ± 6 vs. 96 ± 2 mmHg, NS). Mean heart rate was not affected by bromocriptine (84 ± 2 vs. 83 ± 3 bpm, NS) or placebo (81 ± 1 vs. 86 ± 2 bpm, NS).

CONCLUSIONS — In the present study, 4 months of a quick-release formulation of bromocriptine treatment significantly lowered FPG and glycosylated hemoglobin concentrations and improved glucose tolerance in obese type 2 diabetic patients. The decline in HbA_{1c} and FPG concentrations was evident within 4 weeks after the start of bromocriptine and remained at this level for the remainder of the 4-month treatment period (Fig. 1). In contrast, the placebo-treated group, after an initial slight decline in HbA_{1c} and fasting plasma glucose during the first month, displayed a progressive rise during the last 3 months of the study. The magnitude and the time course of deterioration in glycemic control in the placebo group are similar to that observed in other placebo-controlled studies (28,29). Moreover, such a time-related deterioration in glycemic control is not surprising considering the severity of obesity and insulin resistance in the present subject population.

In some studies in humans (15,17) and animals (11,13), bromocriptine administration was associated with significant reductions in body weight and percent body fat. Because weight loss is known to enhance insulin sensitivity (30), we took special care to ensure that body weight and body fat content remained stable throughout the 4-month treatment period. Because increased intra-abdominal fat has been shown to be associated with insulin resistance (31), we also quantitated abdominal visceral and subcutaneous fat mass in each subject before and after 4 months of treatment using MRI (21). In the bromocriptine group, baseline visceral fat mass was greater than that in the placebo group. No change from baseline in either visceral or subcutaneous abdominal fat was observed in the bromocriptine- and placebo-treated groups. Therefore, one cannot explain the beneficial effects of bromocriptine on insulin sensitivity and glucose homeostasis by changes in body weight, body composition, or regional fat distribution.

The present results are consistent with data obtained in many vertebrate species (11–13), including humans (15,17), which have shown that bromocriptine administration improves glucose tolerance in nondiabetic obese animals and humans. Moreover, the present findings extend previous observations to obese patients with type 2 diabetes and demonstrate for the first time in humans the clinical usefulness of bromocriptine in the treatment of individuals with type 2 diabetes. Although there were relatively more sulfonylurea-treated patients in the placebo- versus bromocriptine-treated group (the difference was not statistically significant), we do not think that this could have affected our results, because bromocriptine reduced the HbA_{1c} similarly in sulfonylurea- and non-sulfonylurea-treated diabetic subjects.

Bromocriptine failed to significantly improve whole-body insulin-mediated glucose disposal during the first step of the insulin clamp, although maximally insulin-stimulated glucose disposal was augmented by 24% (Fig. 3). Our failure to observe a significant improvement in insulin sensitivity to physiological levels of hyperinsulinemia is consistent with the results of Kamath et al. (16). Using the modified insulin suppression test, these investigators also failed to observe an improvement in insulin sensitivity in nondiabetic insulin-resistant obese subjects after 8 weeks of bromocriptine treatment. Other studies in obese nondiabetic (15,32) and obese diabetic subjects (33) have also shown significant decreases in postmeal glucose excursions throughout the day after bromocriptine treatment. In the present study, bromocriptine had no effect on either the basal rate of EGP or insulin-mediated suppression of EGP. However, it is important to realize that an effect of bromocriptine on the liver could have easily been missed, because the insulin infusion rate during the first step of the insulin clamp produced plasma insulin levels that would be expected to maximally inhibit EGP (1,34). Bromocriptine also failed to increase basal or glucose-stimulated plasma insulin/C-peptide levels, although one could argue that unchanged plasma insulin levels with a reduction in plasma glucose concentration indicates enhanced β-cell sensitivity to glucose. Because bromocriptine did not improve glucose disposal in response to physiological hyperinsulinemia or augment plasma insulin levels, one can ask what mechanism(s) might be responsible for the improvement in OGTT and mean daylong glycemic control, as reflected by the reduction in $HbA_{1c.}$

After a mixed meal, insulin secretion is stimulated, and the resultant hyperinsulinemia plus hyperglycemia suppress EGP and stimulate glucose uptake by peripheral (primarily muscle) and splanchnic (primarily liver) tissues. The present results argue against an effect of bromocriptine to enhance peripheral tissue glucose disposal in response to physiological hyperinsulinemia and exclude an increase in circulating plasma insulin levels. Because the steady-state plasma insulin concentration during the first insulin clamp step is well above that required to observe a maximal suppression of EGP (34), an improvement in postmeal insulin-mediated suppression of EGP by

bromocriptine cannot be excluded. Moreover, after the oral route of glucose administration, suppression of EGP is much less complete than during a 40 $mU \cdot m^{-2} \cdot min^{-1}$ euglycemic insulin clamp (35). Therefore, it is possible that bromocriptine could lower the postmeal glucose excursion by enhancing hepatic sensitivity to insulin. Consistent with this hypothesis, bromocriptine is known to potentiate insulin-mediated suppression of hepatic glucose production during the normal feeding cycle in obese insulin-resistant rodents (14,36). Animal studies indicate that increased ventromedial hypothalamic noradrenergic drive increases hepatic glucose output and causes glucose intolerance, both of which can be improved by bromocritpine treatment (36,37). Because insulin-mediated suppression of postprandial hepatic glucose production is impaired in type 2 diabetic individuals (1,38), it is possible that bromocriptine may potentiate the postmeal inhibition of hepatic glucose production.

Under euglycemic conditions, insulin (at portal concentrations >1,000 μU/ml) does not enhance splanchnic glucose uptake (39). In contrast, after glucose ingestion, approximately one-third of the administered glucose is taken up by the splanchnic region (35). Therefore, it remains a possibility that the reduction in postmeal glucose excursion and mean daylong plasma glucose level after bromocriptine treatment is secondary to enhanced splanchnic glucose uptake. Studies using the dual-isotope technique (35,39) would be of interest to examine the effect of bromocriptine on suppression of hepatic glucose production and splanchnic glucose uptake after glucose ingestion.

Lastly, it is possible that bromocriptine improves postmeal glucose levels and reduces the HbA_{1c} by enhancing glucose-mediated glucose uptake. Because the insulin clamp was carried out under euglycemic conditions, this possibility was not examined in the present study.

In conclusion, timed bromocriptine administration improves glycemic control and glucose tolerance in obese type 2 diabetic patients. The beneficial effect of bromocriptine on glucose homeostasis is not related to enhanced insulin-mediated glucose disposal or a reduction in basal EGP. Potential unexplored mechanisms by which bromocriptine reduces the mean daylong plasma glucose level include enhanced suppression of EGP and/or increased splanchnic glucose uptake after glucose ingestion. Bromocriptine administration offers a novel approach to the treatment of obese individuals with type 2 diabetes and provides new insights for future investigation.

Acknowledgments — The authors would like to thank Magda Ortiz, Diane Frantz, and Janet Shapiro for providing skilled nursing care for our patients and for assisting in the many metabolic studies. Lorrie Albarado provided expert secretarial assistance. The studies described in this article were supported by a grant from Ergo Science.

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