Effect of the New Oral Antidiabetic Agent (−)-BM 13.0913.Na on Insulin Resistance in Lean and Obese Zucker Rats

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The new antidiabetic agent (−)-BM 13.0913.Na (BM) was administered to 12-week-old lean and obese Zucker rats, an animal model of insulin resistance, at a daily dose of 50 mg/kg for 14 days. Hyperinsulinemic-euglycemic clamps were performed on treated and untreated lean and obese Zucker rats. Basal hepatic glucose production (HGP) rates were similar in lean and obese untreated animals. Insulin-induced suppression of HGP was significantly less effective in obese animals. In addition, these animals exhibited the characteristic impaired glucose utilization. In obese animals, drug treatment improved insulin suppression of HGP and total glucose utilization (GU) during clamp studies. Furthermore, drug treatment decreased insulin levels during clamp studies, suggesting an acceleration of insulin clearance. Drug treatment also decreased basal plasma insulin levels and serum and liver concentrations of cholesterol in both fasted lean and obese rats. Additionally, blood glucose, plasma nonesterified fatty acids (NEFA), and serum triglyceride levels were reduced in fasted obese rats, but only minor changes in liver triglycerides were observed in lean and obese rats. On the basis of these results, we suggest that BM is an effective antidiabetic agent that may reduce abnormalities of glucose and lipid metabolism.

DEFECTS IN INSULIN action and secretion and increased hepatic glucose production (HGP) are present in non–insulin-dependent diabetes mellitus.[1] Regardless of which of these abnormalities are primary and which are secondary, it is acknowledged that insulin resistance is a characteristic feature in non–insulin-dependent diabetes mellitus patients, which suggests the need to develop drugs to reduce insulin resistance.

Current treatment for non–insulin-dependent diabetes mellitus uses sulfonylureas and the biguanide drug metformin; these are the only approved oral hypoglycemic agents. Metformin improves glucose tolerance by enhancing tissue sensitivity to insulin,[2] whereas sulfonylureas stimulate insulin release from pancreatic β cells.[3] In 1982, Sohda et al[4] reported on a series of thiazolidinediones that enhance insulin sensitivity. Since then, numerous additional thiazolidinediones have been developed.[5]

(−)-BM 13.0913.Na [(−)-2-(4-methylphenoxy)-7-(4-chlorophenyl)-heptanic acid, sodium salt] (BM) is a new oral agent of a class of compounds with a structure not related to thiazolidinediones. In the accompanying report,[6] we describe the stereoselective antihyperglycemic and antihyperinsulinemic effects of BM in ob/ob mice, db/db mice, yellow KK mice, and streptozotocin-diabetic rats. The results obtained in these animal models suggest a peripheral site of action. The aim of the current study was to prove this supposition by investigating the effect of BM on carbohydrate and lipid metabolism in Zucker rats. The genetically obese Zucker (fa/fa) rat is characterized by mild hyperglycemia, abnormal oral glucose tolerance[7] caused by impaired suppression of HGP following ingestion of glucose,[8] and insulin resistance of both the liver and skeletal muscle tissues.[9] Hence, this is a widely used animal model of insulin resistance. To elucidate the site of action of BM, we compared lean and obese Zucker rats with and without drug treatment using the hyperinsulinemic-euglycemic clamp technique.[10]

MATERIALS AND METHODS

Animals

Genetically obese (fa/fa) and lean (FA/?) male Zucker rats were obtained from Harlan (Austerlitz, The Netherlands), housed in standard animal cages on a 12-hour light/dark cycle, and given free access to water and rat chow (Ssniff Rattendiät, Ssniff Spezialdiäten, Soest, Germany). The animals were allowed to acclimate for at least 5 days before any treatment was started. BM was suspended in 1% tylose and administered by oral gavage to 12-week-old lean and obese Zucker rats at a daily dose of 50 mg/kg for 14 days. Twelve-week-old lean and obese control rats were given only vehicle by oral gavage.

Hyperinsulinemic-Euglycemic Clamp Studies

Four to 7 days before the clamp studies started, rats were anesthetized by inhalation of a combination of Penthrane and Ethrane (Abbott, Wiesbaden, Germany). One catheter was inserted into a femoral artery for blood sampling, and two catheters were inserted into a jugular vein for infusion of glucose solution at a variable rate and 3-[^{3}H]glucose and insulin solution at constant rates. Food was withdrawn approximately 24 hours before the experiment. The glucose clamp was performed in unrestrained conscious rats to avoid the effect of anesthesia. Rats that were not used in clamp studies were deprived of food for 24 hours before killing and subsequent blood collection for determination of insulin, glucose, triglycerides, cholesterol, and nonesterified fatty acids (NEFA). Clamp studies were preceded by collection of a 400-μL blood sample to determine basal blood glucose and plasma immunoreactive insulin. In the basal state, rats received a priming dose of 5 μCi 3-[^{3}H]glucose (New England Nuclear, Dreieich, Germany) followed by a continuous infusion (0.05 μCi/min) until the end of the study. Sixty minutes after beginning the tracer infusion, a priming dose (three times the continuous insulin infusion rate) of porcine monocomponent insulin (Novo Nordisk, Mainz, Germany) was infused for 15 minutes, followed by a continuous insulin infusion of either 18 or 60 pmol · kg^{-1} · min^{-1} for 75 minutes. Infusion of unlabeled glucose (40% solution wt/vol) was begun 5 minutes after starting the insulin infusion. Glucose infusion rates were adjusted to maintain blood glucose values of 100 mg/dL. The steady-state plasma insulin level and blood

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Submitted March 2, 1994; accepted July 6, 1994.

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0026-0495/95/4405-0004$03.00/0

glucose level were established approximately 30 minutes after starting the insulin infusion. During the insulin infusion, arterial blood was sampled every 5 minutes, and blood glucose concentration was determined to adjust glucose infusion rates. In addition, blood was sampled at 30, 50, and 60 minutes in the basal state and at 90, 110, 120, 135, and 150 minutes during insulin infusion for determination of plasma glucose and plasma tracer concentration. Plasma insulin level was measured in samples collected at 60, 80, 100, 120, 135, and 150 minutes.

Glucose Utilization and HGP

A steady state of glucose specific activity was reached after approximately 30 minutes both in the basal-state studies and after beginning the insulin infusion. The rate of glucose disappearance was then equal to the rate of glucose appearance, and this was calculated according to the method reported by Steele[11] by dividing the 3-[^{3}H]glucose infusion rate by the steady-state value for glucose specific activity. Glucose disappearance in the basal state, as well as during insulin infusion, is equal to glucose utilization (GU). In the basal state, HGP is equal to the rate of glucose disappearance. During insulin infusion, the rate of HGP was calculated by subtracting the exogenous glucose infusion rate from the glucose disappearance rate.

Analytical Techniques

Blood glucose and plasma glucose were determined by the hexokinase method[12] using a Gluco-quant test-combination (Boehringer Mannheim, Mannheim, Germany) on an Eppendorf photometer 1101M or on an Epos Analyzer 5060 (Eppendorf Gerätebau, Hamburg, Germany). Blood samples for determination of specific activity of 3-[^{3}H]glucose were deproteinized with 0.3 mol/L $HClO_4$ and immediately centrifuged. An aliquot of the supernatant was used for determination of glucose concentration using the hexokinase method.[12] Plasma 3-[^{3}H]glucose radioactivity was determined in a liquid scintillation counter by measurement of another aliquot of the supernatant after evaporation to dryness to remove tritiated water. Immunoreactive insulin was estimated using the Insulin-RIA-Kit 100 (Pharmacia Diagnostics, Uppsala, Sweden). Triglycerides, cholesterol, and NEFA in serum were determined on an Epos Analyzer 5060 by enzymatic assays using kits purchased from Boehringer and Wako Chemicals (Neuss, Germany). Triglycerides and cholesterol in liver were extracted with Folch-Sperry solution. Triglycerides were saponified with ethanolic KOH and determined photometrically as previously described.[13,14] Cholesterol was assayed according to the method reported by Siedel et al.[15]

Statistical Analysis

Results are presented as the mean ± SEM for the indicated number of rats. Comparisons within groups were made using a paired *t* test, and comparisons between groups were made using an unpaired two-tailed *t* test (StatView II, Abacus Concepts, Calabasas, CA). Differences were considered statistically significant at P less than .05.

RESULTS

Baseline Characteristics

Characteristics of animals used in the study are listed in Table 1. Lean and obese BM- or vehicle-treated rats in which clamp studies were performed were chosen at random and, as a whole, showed no significant differences from the corresponding subset of animals.

After the 14-day course of treatment, body weights of obese rats and lean control rats had increased significantly. By contrast, BM-treated lean rats had stopped gaining weight.

Fasting insulin and glucose concentrations were significantly higher in obese vehicle-treated versus lean vehicle-treated animals ($P < .001$). In lean animals, drug treatment appeared to have no effect on blood glucose levels. In obese animals, drug treatment significantly decreased blood glucose concentrations ($P < .05$ *v* vehicle-treated obese rats). Nonetheless, glucose concentrations were still slightly higher than in lean animals ($P < .05$).

Drug treatment markedly decreased insulin concentrations in both lean ($P < .001$ *v* vehicle-treated lean rats) and obese ($P < .05$ *v* vehicle-treated obese rats) animals, but

Table 1. Weight Changes and Insulin Values in Fasted BM-Treated and Vehicle-Treated Rats

Groups	Weight (g)		Blood Glucose (mmol/L)	Immunoreactive Insulin (pmol/L)
	Pretreatment	Posttreatment		
Lean vehicle-treated				
Without clamp (n = 53)	276 ± 3	295 ± 4#	5.4 ± 0.1 (n = 33)	81 ± 9
With clamp (n = 15)	265 ± 4	279 ± 6**	5.3 ± 0.1	94 ± 16
Lean BM-treated				
Without clamp (n = 56)	287 ± 5	288 ± 4	5.3 ± 0.2 (n = 28)	45 ± 4 (n = 49)‡
With clamp (n = 13)	282 ± 6	275 ± 4	5.0 ± 0.2	33 ± 2‡
Obese vehicle-treated				
Without clamp (n = 43)	384 ± 5	435 ± 8‡	6.8 ± 0.2 (n = 30)§	489 ± 47§
With clamp (n = 14)	372 ± 10	409 ± 14**	6.4 ± 0.3§	461 ± 55§
Obese BM-treated				
Without clamp (n = 65)	383 ± 4	432 ± 5#	6.0 ± 0.2 (n = 32)†¶	305 ± 29 (n = 53)†‖
With clamp (n = 19)	375 ± 5	412 ± 8#	5.5 ± 0.3*	322 ± 40*‖

NOTE. Values are the mean ± SEM.

*$P < .05$, †$P < .01$, ‡$P < .001$: *v* vehicle-treated control rats.

§$P < .001$ *v* lean vehicle-treated rats.

‖$P < .001$ *v* lean BM-treated rats.

¶$P < .05$ *v* lean BM-treated rats.

#$P < .001$ *v* pretreatment weight.

**$P < .05$ *v* pretreatment weight.

concentrations remained higher in obese as compared with lean animals ($P < .001$).

Hyperinsulinemic-Euglycemic Clamp Studies

Steady-state insulin concentrations. Due to the insulin infusion, insulin levels increased significantly in both obese and lean animals (Fig 1). Steady-state insulin levels at the lower rate of insulin infusion were significantly higher in obese vehicle-treated rats as compared with lean vehicle-treated rats (1,482 ± 286 *v* 541 ± 23 pmol/L, $P < .05$). In comparison to levels in lean control rats, insulin concentrations in obese vehicle-treated rats were also increased at the insulin infusion rate of 60 pmol · kg^{-1} · min^{-1} (3,516 ± 350 *v* 2,568 ± 330 pmol/L). However, the difference was not statistically significant. After drug treatment, steady-state insulin levels during the insulin infusion rate of 18 pmol · kg^{-1} · min^{-1} were significantly lower in both lean and obese animals than in vehicle-treated animals (312 ± 42 *v* 541 ± 23 pmol/L in lean rats and 672 ± 101 *v* 1,482 ± 286 pmol/L in obese rats, $P < .05$). At the higher insulin infusion rate, steady-state insulin concentrations were lower in both lean and obese BM-treated rats than in vehicle-treated rats. However, steady-state insulin levels were significantly decreased only in lean BM-treated animals (1,656 ± 235 *v* 2,568 ± 330 pmol/L in lean rats, $P < .05$). Insulin levels remained significantly higher in obese BM-treated rats than in lean BM-treated rats at the lower

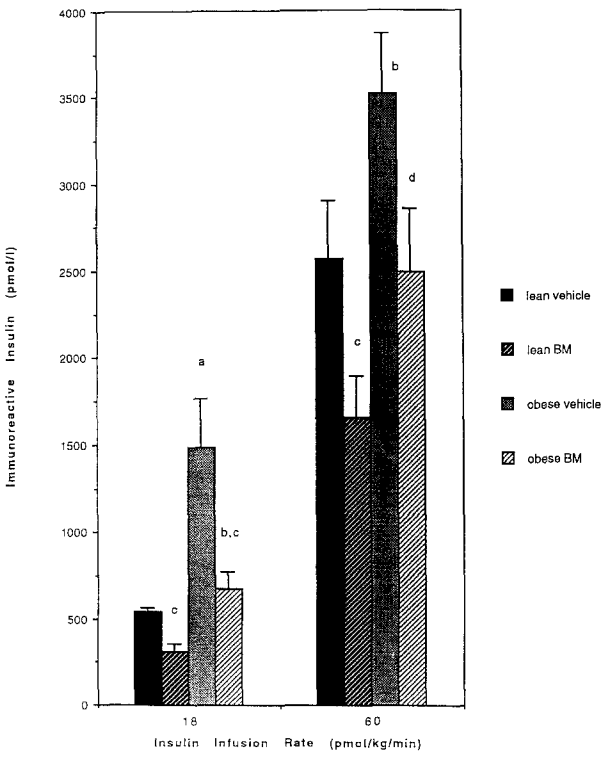

Fig 1. Insulin levels during insulin infusion. Values are the mean ± SEM. (■) Lean vehicle-treated rats; (▨) lean BM-treated rats; (▩) obese vehicle-treated rats; (▧) obese BM-treated rats. [a]*P* < .05 *v* lean vehicle-treated rats; [b]NS *v* lean vehicle-treated rats; [c]*P* < .05 *v* vehicle-treated control rats; [d]NS *v* lean and obese vehicle-treated rats and lean BM-treated rats.

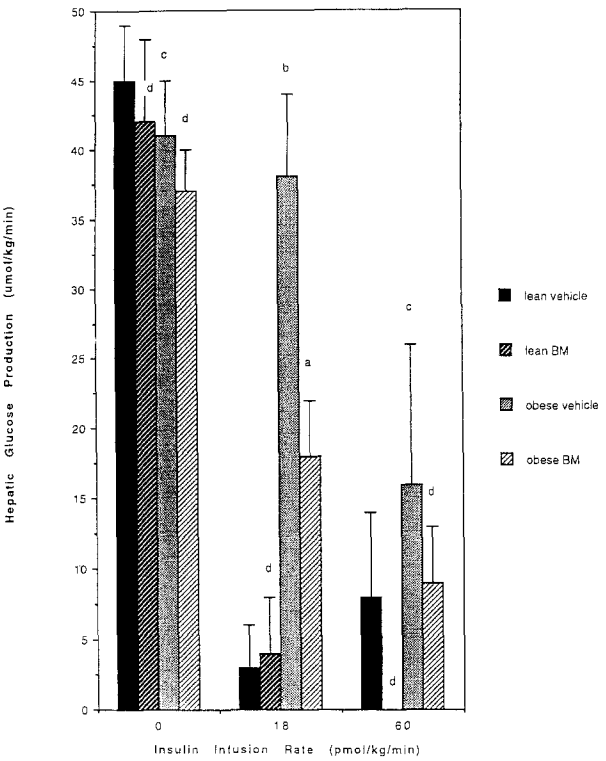

Fig 2. HGP. Values are the mean ± SEM. (■) Lean vehicle-treated rats; (▨) lean BM-treated rats; (▩) obese vehicle-treated rats; (▧) obese BM-treated rats. [a]*P* ± .05 *v* vehicle-treated control rats; [b]*P* ± .001 *v* lean vehicle-treated rats; [c]NS *v* lean vehicle-treated rats; [d]NS *v* vehicle-treated control rats.

insulin infusion rate (672 ± 101 *v* 312 ± 42 pmol/L, $P < .05$). Nevertheless, there was no significant difference between insulin concentrations in obese BM-treated rats versus lean vehicle-treated rats (672 ± 101 *v* 541 ± 23 pmol/L). Moreover, at the insulin infusion rate of 60 pmol · kg^{-1} · min^{-1}, differences between insulin levels in obese BM-treated rats and both BM-treated and vehicle-treated lean rats were not significant.

HGP. As shown in Fig 2, basal rates of HGP in lean (45 ± 4 μmol · kg^{-1} · min^{-1}) and obese (41 ± 4) vehicle-treated animals were similar. After drug treatment, basal rates of HGP in lean (42 ± 6 μmol · kg^{-1} · min^{-1}) and obese (37 ± 3) rats were slightly but not significantly decreased as compared with vehicle-treated animals. With the insulin infusion rate of 18 pmol · kg^{-1} · min^{-1}, suppression of HGP was significantly less in obese vehicle-treated animals as compared with lean animals (38 ± 6 *v* 3 ± 3 μmol · kg^{-1} · min^{-1}, $P < .001$).

Insulin-induced suppression of HGP in obese vehicle-treated rats was not statistically significantly impaired at the higher insulin infusion rate in comparison to HGP in lean vehicle-treated rats (16 ± 10 *v* 8 ± 6 μmol · kg^{-1} · min^{-1}). As compared with basal HGP, no significant suppression of HGP occurred with the insulin infusion rate of 18 pmol · kg^{-1} · min^{-1} in obese vehicle-treated rats. Drug treatment improved the impaired insulin-induced suppression of HGP in obese animals ($P < .05$ *v* obese control rats at 18 pmol · kg^{-1} · min^{-1} , NS *v* obese control rats at 60

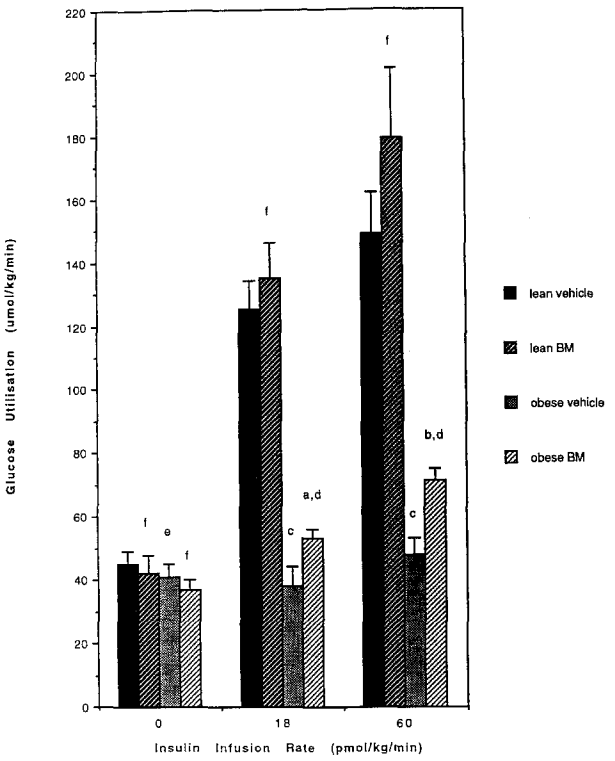

Fig 3. GU. Values are the mean ± SEM. (■) Lean vehicle-treated rats; (▨) lean BM-treated rats; (▩) obese vehicle-treated rats; (▨) obese BM-treated rats. [a]P ± .05, [b]P ± .01 *v* vehicle-treated control rats; [c]P ± .001 *v* lean vehicle-treated rats; [d]P ± .001 *v* lean BM-treated rats; [e]NS *v* lean vehicle-treated rats; [f]NS *v* vehicle-treated control rats.

pmol · kg^{-1} [6dd] Z min^{-1}), but did not affect basal HGP in lean and obese rats. HGP was not significantly altered in drug-treated lean rats as compared with vehicle-treated lean rats at both rates of insulin infusion.

GU. As mentioned earlier, basal HGP was similar in the four subsets of animals (lean BM- or vehicle-treated and obese BM- or vehicle-treated). This indicates that basal GU was also similar. As shown in Fig 3, GU in vehicle-treated animals was significantly lower in obese rats than in lean rats at both rates of insulin infusion (P < .001). Insulin infusion in obese vehicle-treated rats even failed to increase GU significantly above the basal GU. After drug treatment, GU was slightly but not significantly increased in lean animals at both insulin infusion rates, whereas in obese animals, drug treatment resulted in a significantly increased GU at both insulin infusion rates (P < .05 *v* obese control group at 18 pmol · kg^{-1} · min^{-1}, P < .01 *v* obese control group at 60 pmol · kg^{-1} · min^{-1}). Despite this increased GU, obese BM-treated rats still had reduced uptake as compared with lean rats.

Effects on lipid metabolism. As shown in Table 2, triglycerides, cholesterol, and NEFA levels were significantly (P < .001) higher in obese control rats as compared with lean vehicle-treated rats. Drug treatment significantly decreased serum cholesterol in lean (P < .001) and obese (P < .01) rats, as well as serum NEFA (P < .05) and triglycerides (P < .001) in obese rats. Despite the decrease in triglycerides, cholesterol, and NEFA levels in drug-treated obese rats, they did not reach normal levels in lean rats.

Triglyceride levels in the liver of fa/fa rats (Table 3) were significantly higher than in FA/? rats (P < .001). Drug treatment induced only marginal changes in triglyceride values in the liver of both lean and obese rats. Cholesterol levels in the liver of vehicle-treated lean and obese animals were similar (Table 3). After drug treatment, cholesterol values in the liver of both fa/fa and FA/? rats were significantly lower than in vehicle-treated rats (P < .001). The effect of decreasing cholesterol in the liver was significantly more pronounced in obese BM-treated rats than in lean BM-treated rats (P < .01).

DISCUSSION

In the accompanying report, we describe the effect of BM on insulin, carbohydrate, and lipid metabolism in different animal models.[6] In these studies, we showed that genetically obese yellow KK mice, ob/ob mice, and diabetic db/db mice responded to drug treatment with a significant reduction in hyperglycemia and hyperinsulinemia. Low-dose streptozotocin-diabetic rats, another model of insulin resistance, also showed improved insulin sensitivity after drug treatment. The studies suggest a peripheral site of action.

To elucidate the site of action of BM, we performed a study in the genetically obese fa/fa rat. The fa/fa rat is a widely used model to study the potential of drugs to improve insulin sensitivity because this animal model of insulin resistance shows only mild glucose intolerance,[7,8] and the sites of insulin resistance[9,16,17] are similar to those

Table 2. Triglycerides, Cholesterol, and NEFA Values in Serum of Fasted BM-Treated and Vehicle-Treated Rats

Groups	Triglycerides (g/L)	Cholesterol (mmol/L)	NEFA (g/L)
Lean			
Vehicle-treated (n = 27)	0.63 ± 0.08	1.91 ± 0.06	0.1 ± 0.01 (n = 9)
BM-treated (n = 38)	0.75 ± 0.05	1.15 ± 0.07‡	0.14 ± 0.01 (n = 11)
Obese			
Vehicle-treated (n = 23)	3.56 ± 0.41§	3.12 ± 0.13§	0.29 ± 0.09 (n = 11)§
BM-treated (n = 40)	1.76 ± 0.16‡‖	2.57 ± 0.10†‖	0.20 ± 0.03 (n = 13)*¶

NOTE. Values are the mean ± SEM. NEFA are calculated with reference to oleic acid.

*P < .05, †P < .01, ‡P < .001: *v* vehicle-treated control rats.

§P < .001 *v* lean vehicle-treated rats.

‖P < .001 *v* lean BM-treated rats.

¶P < .05 *v* lean BM-treated rats.

Table 3. Triglyceride and Cholesterol Values in Liver of Fasted BM-Treated and Vehicle-Treated Rats

Groups	Triglycerides (g/100 g liver)	Cholesterol (mmol/100 g liver)
Lean		
Vehicle-treated	1.36 ± 0.12 (n = 13)	6.98 ± 0.16 (n = 23)
BM-treated	1.42 ± 0.12 (n = 18)‖	5.31 ± 0.18 (n = 19)*
Obese		
Vehicle-treated	2.80 ± 0.14 (n = 13)†	6.62 ± 0.35 (n = 19)¶
BM-treated	2.65 ± 0.16 (n = 17)‡‖	4.69 ± 0.10 (n = 22)*§

NOTE. Values are the mean ± SEM.
*$P < .001$ *v* vehicle-treated control rats.
†$P < .001$ *v* lean vehicle-treated rats.
‡$P < .001$ *v* lean BM-treated rats.
§$P < .01$ *v* lean BM-treated rats.
‖NS *v* vehicle-treated control.
¶NS *v* lean vehicle-treated rats.

reported in patients with non–insulin-dependent diabetes mellitus. We used 12-week-old lean and obese Zucker rats, since we were able to show in previous in vivo studies that fa/fa rats should be approximately 12 weeks old if they are to be used as a model for showing how insulin-sensitizing agents might reduce insulin resistance and glucose intolerance. This is because insulin resistance and glucose intolerance are almost fully developed in fa/fa rats of this age, and because other interfering traits are less pronounced than in older rats.[18]

In accordance with the findings reported by Terrettaz et al,[9] we observed in our study a similar basal HGP and glucose metabolism in both vehicle-treated lean and obese rats, as well as an impaired insulin-induced suppression of HGP and no significant effect of insulin infusion on GU in vehicle-treated obese rats. BM treatment induced a significant increase in insulin-stimulated GU and suppressed HGP in insulin-resistant, genetically obese fa/fa rats. The experiments with 3-[^{3}H]glucose as tracer evidenced a similar rate of glucose turnover in BM-treated and vehicle-treated lean and obese animals, whereas GU was significantly higher in obese BM-treated rats in comparison to obese vehicle-treated rats at both insulin infusion rates. This fact, which was observed despite lower basal and clamp insulin concentrations, reflects improved insulin sensitivity in obese BM-treated rats. Nevertheless, a defect was still present in BM-treated fa/fa rats as compared with lean rats. The data also suggest that the improved insulin sensitivity in fa/fa rats involves both the liver and peripheral tissues, since insulin-mediated suppression of HGP and stimulation of peripheral glucose uptake were significantly enhanced by BM treatment.

In lean animals, GU and suppression of HGP were similar in BM-treated and vehicle-treated rats, although in lean and obese rats decreased insulin levels were measured during the clamp. Furthermore, we were able to demonstrate that BM does not produce hypoglycemia in lean rats at a dose that is maximally effective at decreasing hyperglycemia in ob/ob mice.[6] This indicates that BM can enhance insulin sensitivity in both diabetic and nondiabetic animals without producing hypoglycemia. Insulin action and plasma insulin concentrations seem to be coordinated in such a way that enhanced insulin action in normal rats is accompanied by a reduction in plasma insulin levels to prevent hypoglycemia. Similar observations after BM treatment were made in yellow KK mice and ob/ob mice.[6] As mentioned earlier, we found a reduction in basal insulin levels in BM-treated obese rats; during the clamp studies, we observed lower insulin concentrations in BM-treated rats than in vehicle-treated rats, although equivalent doses of insulin were infused. This can partially be explained by the lower basal insulin levels in BM-treated rats, but an effect of BM on insulin clearance cannot be ruled out. Interestingly, thiazolidinedione derivatives have been reported to produce similar reductions in insulin levels.[19-24]

Carbohydrate metabolism is not the only pathway affected by insulin resistance. Hyperlipemia is also a common trait in obesity and diabetes. Drug treatment significantly decreased serum NEFA and triglyceride levels in fasted obese fa/fa rats. Possibly, the improved insulin-stimulated suppression of HGP and the improved glucose uptake in skeletal muscle leads to a reduced supply of glucose in the liver and white adipose tissue and consequently to reduced lipogenesis. This hypothesis is supported by the observation that the decrease in triglyceride and NEFA concentrations in serum of BM-treated yellow KK mice, ob/ob mice, or db/db mice was preceded by a reduction in glucose concentrations.[6] The decreased NEFA levels may in turn contribute to the hypoglycemic effect of BM, because NEFA can reduce glucose uptake in peripheral tissues,[1,25,26] as well as potentiate glucose production by the liver.[1,27] The decreased serum NEFA values observed in BM-treated fa/fa rats may be caused by attenuated release of NEFA from adipose tissue as a result of the beneficial antilipolytic effects of insulin as the consequence of a generally reduced insulin resistance.

The decreased serum triglyceride levels in fa/fa rats may be caused by decreased hepatic triglyceride production. The BM-induced reduction in hyperinsulinemia could be another reason for the decrease in blood triglycerides, since hyperinsulinemia in the insulin-resistant state may cause hypertriglyceridemia as a result of increased hepatic triglyceride output. Insulin is a potent stimulator of lipid synthesis, and moreover, hepatic triglyceride production still seems to be insulin-sensitive in fa/fa rats.[28] Since NEFA in blood serve as precursors for hepatic triglyceride synthesis,[29] a decrease in blood NEFA levels could also contribute to decreased triglyceride synthesis in the liver.

Another interesting aspect is the significant decrease of cholesterol levels in the liver and serum of BM-treated lean and obese rats. This effect was not observed in BM-treated yellow KK mice, ob/ob mice, or db/db mice.[6] Since concentrations of circulating triglycerides and high-density lipoprotein (HDL) cholesterol are inversely related,[30] it seems possible that the effect of decreasing serum triglycerides may in some way be responsible for the reduction in serum cholesterol values. The existence of a positive correlation between HDL cholesterol and lipoprotein lipase activity led Magill et al[31] to postulate that the inverse relationship between circulating triglycerides and HDL cholesterol may be due to differences in lipoprotein lipase activity. Accord-

ing to this hypothesis, increasing lipoprotein lipase activity would enhance very–low-density lipoprotein catabolism, which in turn accelerates the transfer of surface material to HDL, thus increasing HDL cholesterol concentration. Since lean BM-treated rats did not show diminished triglyceride values despite decreased cholesterol levels, the latter mechanism seems unlikely.

A further mechanism would be the reduced absorption of dietary cholesterol, as reported for pioglitazone, a thiazolidinedione derivative, by Colca et al.[32] However, these investigators found a cholesterol-lowering effect in rats with streptozotocin-induced diabetes fed a high-cholesterol diet, but not in quail, mice, or rats fed a normal diet like the animals in our study. Whatever the mechanism, our data suggest that reduction of insulin resistance by treatment with BM has a beneficial effect on circulating cholesterol levels.

An unexpected observation in our study was that BM-treated lean rats had stopped gaining weight. This effect was seen in all BM-treated lean rats, but not in obese rats. Our BM-treated lean animals appeared healthy and continued to eat and drink during the period of treatment. Since we do not have data on actual food consumption, conclusions regarding the etiology of this observation are impossible. Interestingly, Bowen et al[19] reported a drug-induced weight loss of unknown etiology in lean Zucker rats after treatment with the thiazolidinedione derivative CP 68,722.

In summary, BM is a new oral antidiabetic agent that enhances hepatic and peripheral sensitivity to insulin without producing hypoglycemia and improves glucose tolerance and lipid metabolism. On the basis of these observations, we suggest that BM may be an antidiabetic agent with desirable effects on glucose and lipid metabolism in non–insulin-dependent diabetes mellitus patients that may have a lower risk of hypoglycemic episodes commonly observed with sulfonylurea therapy.

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