Nongenetic Mouse Models of Non–Insulin-Dependent Diabetes Mellitus

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The purpose of the study was to develop a mouse model of non–insulin-dependent diabetes mellitus (NIDDM) that closely simulates the metabolic abnormalities of the human disease and is also cost-effective compared with the genetic models currently available. For this purpose, insulin resistance was induced in male C57BL/6J or Institute of Cancer Research (ICR) mice by feeding diets enriched in either fructose or fat, and hyperglycemia was induced by injecting these mice with a dose of streptozotocin (STZ) that does not cause diabetes in chow-fed mice. In the case of C57BL/6J mice, insulin levels initially increased in response to the fructose- and fat-enriched diets and then decreased to levels comparable to or still higher than those in chow-fed mice following STZ injection. Associated with the decrease in insulin levels following STZ, fat-fed and fructose-fed C57BL/6J mice became significantly hyperglycemic, reaching values of 388 ± 38 and 366 ± 58 mg/dL, respectively. In contrast, neither plasma glucose nor insulin concentrations changed in chow-fed mice injected with an identical amount of STZ. Essentially identical findings were seen before and after STZ injection in fat-fed compared with chow-fed ICR mice. Although a direct comparison was not made, sensitivity to the diabetogenic effects of STZ appeared to be greater in fat-fed ICR compared with fat-fed C57BL/6J mice. Finally, plasma glucose decreased when mice with these experimental models of NIDDM were treated with either metformin or tolbutamide. Given these results, it seems reasonable to suggest that the combination of dietary-induced insulin resistance and relatively low-dose STZ results in mouse models that should be of use in studying the pathophysiology of NIDDM or in evaluating therapeutic compounds for the treatment of NIDDM.

ALTHOUGH THE CONTROVERSY continues[1,2] as to the relative roles of insulin resistance and insulin secretion in the pathogenesis of non–insulin-dependent diabetes mellitus (NIDDM), there is considerable evidence that insulin resistance can be discerned in nondiabetic first-degree relatives of patients with NIDDM.[3-5] Normal glucose tolerance is maintained in these subjects because the pancreas is able to secrete enough insulin to overcome the insulin resistance, and frank hyperglycemia does not occur until this compensatory response fails.[6,7] We do not believe that these characteristics are adequately present in rodent models often used to study the pathophysiology of NIDDM or used in the process of drug discovery and evaluation. For example, C57BL/6J obese (ob/ob) and C57BL/ks diabetic (db/db) mice, which are widely used for these purposes, differ in many respects from the typical patient with NIDDM. Indeed, few patients with NIDDM exhibit the degree of obesity that characterizes ob/ob and db/db mice.[8] In addition, hyperglycemic patients with NIDDM do not demonstrate the extreme degree of hyperinsulinemia seen in both mouse models.[8,9] Finally, development of hyperglycemia in ob/ob and db/db mice is genetically determined to a much greater extent than in patients with NIDDM.[8]

The present study was initiated in an effort to develop a new mouse model of NIDDM, based on the premise that the closer it came to sharing the metabolic characteristics of patients with NIDDM, the more relevant and useful it would be. A second goal was to define a mouse model of NIDDM that was less expensive to use and easier to obtain than the genetic models now available to investigators. Our experimental approach was an extension of prior studies showing that fructose-fed and fat-fed rodents became insulin-resistant and hyperinsulinemic but were able to maintain normal glucose homeostasis[10,11]—a condition similar to the prediabetic state in humans.[6,7] We reasoned that administration of relatively low-dose streptozotocin (STZ) to such animals would lead to significant hyperglycemia, whereas the same dose would not decrease the insulin secretory capacity enough to cause hyperglycemia in rodents fed conventional chow. The results presented herein support our hypothesis and describe a mouse model that we believe offers significant advantages in the study of NIDDM.

MATERIALS AND METHODS

Male C57BL/6J mice from Jackson Laboratory (Bar Harbor, ME) and male Institute of Cancer Research (ICR) mice from Charles River Laboratories (Hollister, CA) were obtained at 3 weeks of age and fed on conventional chow or diets enriched in either fat (35.5% wt/wt; Bioserv, Frenchtown, NJ) or fructose (60% wt/wt; Harlan Teklad, Madison, WI). The composition of the diets is listed in Table 1. The mice were housed (five per cage) in a temperature (22° ± 3°C)- and humidity (50% ± 20%)-controlled room with a 12-hour light (6 AM to 6 PM)/dark cycle. After exposure to the respective diets for 3 weeks, mice were injected intraperitoneally with either STZ (Sigma, St Louis, MO) 100 mg/kg body weight or vehicle (0.05 mol/L citric acid, pH 4.5) and kept on the same diet for the next 4 weeks. Under nonfasting conditions, blood was obtained 1, 2, and 4 weeks post-STZ by nipping the distal part of the tail. Samples were used to measure nonfasting plasma glucose and insulin concentrations. Body weight and food intake were recorded weekly.

Additional studies were performed in ICR mice to directly determine the effect of the high-fat diet on the ability of insulin to stimulate glucose disposal. These experiments, initiated at the end of the 7-week period just described, involved three groups of mice: fat-fed or chow-fed injected with vehicle and fat-fed injected with STZ. Mice were fasted for 4 hours before the experiments. In the first series of experiments, mice were anesthetized with methoxyflurane (Pitman-Moor, Mundelein, IL) inhalation. Regular insulin (Sigma) was injected intravenously ([IV] 0.1 U/kg body weight) through a tail vein, and blood was collected 3, 6, 9, 12, and 15 minutes after the injection from a different tail vein. Plasma glucose concentrations were determined on these samples, and the half-life ($t_{1/2}$) of glucose disappearance from plasma was calculated using WinNonlin (Scientific Consulting, Apex, NC), a pharmacokinetics/pharmacodynamics software program.

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Table 1. Diet Composition (% wt/wt)

Ingredient	Regular Chow	High-Fat (lard) Diet	High-Fructose Diet
Fat	4.5	35.5	5
Protein	23	20	20
Carbohydrate			
Starch	31.9	36.4	0.0
Fructose	3.7	0.0	60
Fiber	5.3	0.1	9.4

In the second series of experiments, mice were anesthetized with intraperitoneal sodium pentobarbital (Sigma). The abdominal cavity was opened, and the main abdominal vein was exposed and catheterized with a 24-gauge IV catheter (Johnson-Johnson Medical, Arlington, TX). The catheter was secured to muscle tissue adjacent to the abdominal vein, cut on the bottom of the syringe connection, and hooked to a prefilled PE50 plastic tube, which in turn was connected to a syringe with infusion solution. The abdominal cavity was then sutured closed. With this approach, there would be no blockage of backflow of the blood from the lower part of the body. Mice were infused continuously with glucose (24.1 mg/kg/min) and insulin (10 mU/kg/min) at a infusion volume of 10 μL/min. Retro-orbital blood samples (70 μL each) were taken 90, 105, 120, and 135 minutes after the start of infusion for measurement of plasma glucose and insulin concentrations. The mean of these four samples was used to estimate steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations for each animal.

Finally, experiments to evaluate the ability of metformin (Sigma) and tolbutamide (Sigma) to decrease plasma glucose were performed in the following three groups of STZ-injected mice: (1) fat-fed C57BL/6J, (2) fructose-fed C57BL/6J, and (3) fat-fed ICR. Plasma glucose concentrations of the mice used in these studies were 255 to 555 mg/dL, and mice were randomly assigned to treatment with either vehicle, metformin (250 mg/kg twice daily), or tolbutamide (200 mg/kg twice daily). A total of three doses were administered via the oral route. Tail vein blood samples were taken for measurement of the plasma glucose concentration before the first dose and 3 hours after the final dose at 27 hours.

Plasma glucose concentrations were determined using the Glucose Diagnostic Kit from Sigma (Sigma No. 315), an enzyme colorimetric assay. Plasma insulin levels were determined using the Rat Insulin RIA Kit from Linco Research (#RI-13K; St Charles, MO). Data are expressed as the mean ± SEM, and one-way ANOVA or Student's *t* test were used to assess the statistical significance of differences.

RESULTS

Plasma glucose concentrations before and 1, 2, and 4 weeks after STZ injection in C57BL/6J mice fed chow, high-fat, or high-fructose diets are shown in Fig 1. Plasma glucose was higher in fat-fed mice (253 ± 10 mg/dL) before STZ injection ($P < .01$, one-way ANOVA) compared with either chow-fed (190 ± 5 mg/dL) or fructose-fed (206 ± 8 mg/dL) mice. There was little or no change in the mean plasma glucose concentration at any time following STZ in the chow-fed group, whereas a significant ($P < .01$, one-way ANOVA) increase in plasma glucose was present 4 weeks after STZ in both fructose-fed (366 ± 58 mg/dL) and fat-fed (388 ± 38 mg/dL) mice. However, it should be noted that hyperglycemia seemed to develop earlier following STZ injection in fructose-fed mice, and was significantly higher than the baseline value 1 week after STZ (306 ± 60 *v* 206 ± 8 mg/dL, $P < .05$ by Student's *t* test).

Food intake over the 7-week experimental period, as well as body weight and plasma insulin concentrations at the end of the study, are shown in Table 2. Food intake was higher in fat-fed compared with chow-fed mice (15.4 ± 0.2 *v* 12.6 ± 0.4, $P < .01$), whereas no significant difference was observed between fructose-fed and chow-fed mice. There was no difference in food intake between vehicle- and STZ-treated mice. The body weight at the end of the study approximately paralleled the food intake and was lower in STZ-injected mice in all three

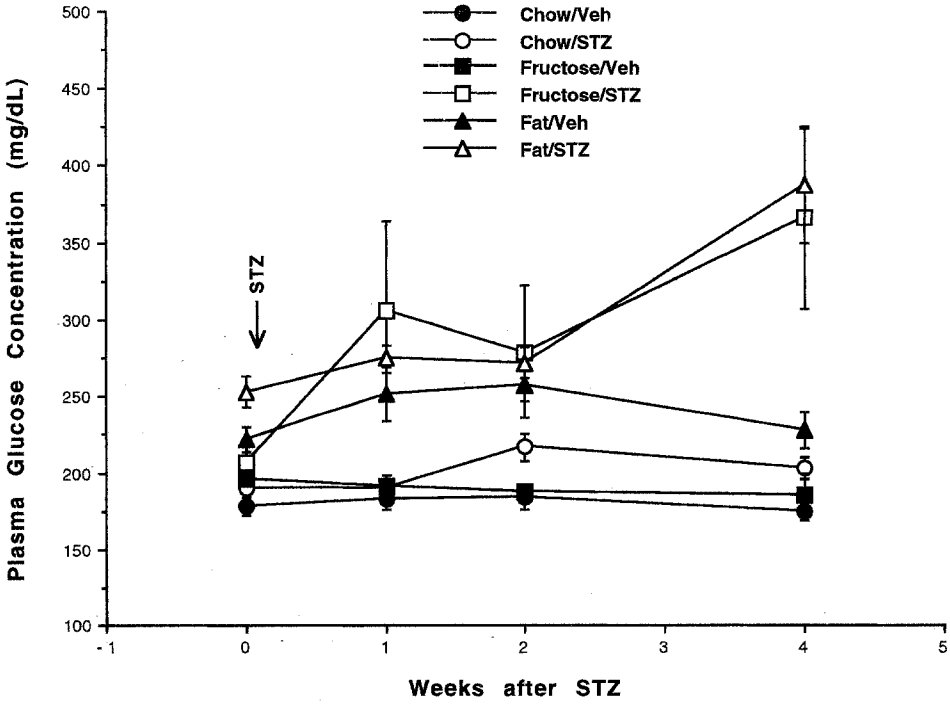

Fig 1. Plasma glucose concentrations before and after STZ injection in C57BL/6J mice. Mice were started on chow or fructose- or fat-enriched diets at age 3 weeks, and plasma glucose concentrations measured 3 weeks later. They were then injected with STZ (time 0) and maintained on the same diets. Plasma glucose concentrations were again measured 1, 2, and 4 weeks later.

Table 2. Food Intake, Body Weight, and Plasma Insulin Concentration in C57BL/6J Mice

Treatment	Food Intake (kcal/mouse/d) Over 7 Weeks	Body Weight (g) Pre-STZ	Body Weight (g) Week 7	Plasma Insulin (μU/mL) Week 7
Chow-fed				
Vehicle	12.6 ± 0.4	19.6 ± 0.3	23.0 ± 0.3	18.2 ± 0.9
STZ	11.3 ± 0.8	19.1 ± 0.4	21.8 ± 0.3	22.0 ± 0.7
Fat-fed				
Vehicle	15.4 ± 0.2*	23.3 ± 0.6	33.6 ± 1.2*	77.1 ± 17.6*‡
STZ	14.1 ± 0.1*	23.6 ± 0.5	29.9 ± 1.0*†	49.8 ± 8.6*†
Fructose-fed				
Vehicle	11.4 ± 0.4	18.8 ± 0.5	22.3 ± 0.5	28.3 ± 1.6*
STZ	12.1 ± 0.4	18.5 ± 0.4	20.7 ± 0.8*	26.7 ± 2.6

*$P < .05$ *v* chow-fed, vehicle-treated mice.
†$P < .05$ *v* corresponding diet, vehicle-treated mice.
‡$P < .05$ *v* fructose-fed, vehicle-treated mice.

groups, where the difference was more significant in fat-fed mice. Plasma insulin levels in vehicle-injected mice were higher in both fat-fed ($P < .01$, one-way ANOVA) and fructose-fed ($P < .01$, one-way ANOVA) versus chow-fed mice. In addition, fat-fed mice had higher insulin concentrations than mice fed fructose ($P < .01$, one-way ANOVA). Insulin levels following STZ did not change substantially in either fructose-fed or chow-fed mice, but decreased by about 30 μU/mL in fat-fed mice.

Studies similar to those just described were also performed in chow-fed and fat-fed ICR mice. Plasma insulin and glucose concentrations before and after STZ in chow-fed and fat-fed ICR mice are shown in Fig 2. Plasma insulin concentrations were significantly increased ($P < .05$) before STZ injection in fat-fed ICR mice. These levels remained significantly elevated in fat-fed ICR mice injected with vehicle, whereas they decreased to the values observed in mice fed regular chow in fat-fed mice injected with STZ. Insulin levels were similar in chow-fed mice injected with either STZ or vehicle.

Plasma glucose concentrations are shown in Fig 2, and it is apparent that the decrease in insulin concentrations following STZ in fat-fed mice was associated within 1 week with an approximate doubling of the plasma glucose concentration ($P < .01$); the change persisted for the remainder of the study. In contrast, plasma glucose concentrations remained essentially stable throughout the study in fat-fed mice injected with vehicle, and in mice fed chow irrespective of whether they were injected with STZ. Body weight was higher at the end of the 7-week study in fat-fed ICR mice injected with vehicle (44.7 ± 1.4 g) compared with the other three groups, which weighed between 36 and 38 g at the end of the study.

The results shown in Figs 1 and 2 strongly suggest that resistance to insulin-mediated glucose disposal develops when either C57BL/6J or ICR mice are fed a fat-enriched diet. To provide experimental support for this interpretation, the effect of a high-fat diet on insulin action was evaluated by two different techniques in fat-fed ICR mice. Figure 3 displays the change in the rate of glucose disappearance from plasma following IV injection of insulin (0.1 U/kg). The $t_{1/2}$ of the glucose disappearance curve was fastest in chow-fed vehicle-injected mice ($t_{1/2}$ = 28 ± 4.4 minutes), intermediate in fat-fed vehicle-injected mice ($t_{1/2}$ = 67 ± 12.6, $P < .01$), and slowest in fat-fed STZ-injected mice ($t_{1/2}$ = 173 ± 38.8, $P < .01$).

To further evaluate the effect of the high-fat diet, SSPI and SSPG concentrations were measured in ICR mice at the end of the continuous infusion of insulin and glucose. The results in Fig 4 show that SSPI concentrations were higher in fat-fed mice ($P < .05$) regardless of whether they were injected with vehicle or STZ. However, despite this, SSPG was higher ($P < .05$) in fat-fed compared with chow-fed rats injected with either vehicle or STZ.

Since one of the goals of the study was to develop a mouse model that would be useful in discovering new compounds for

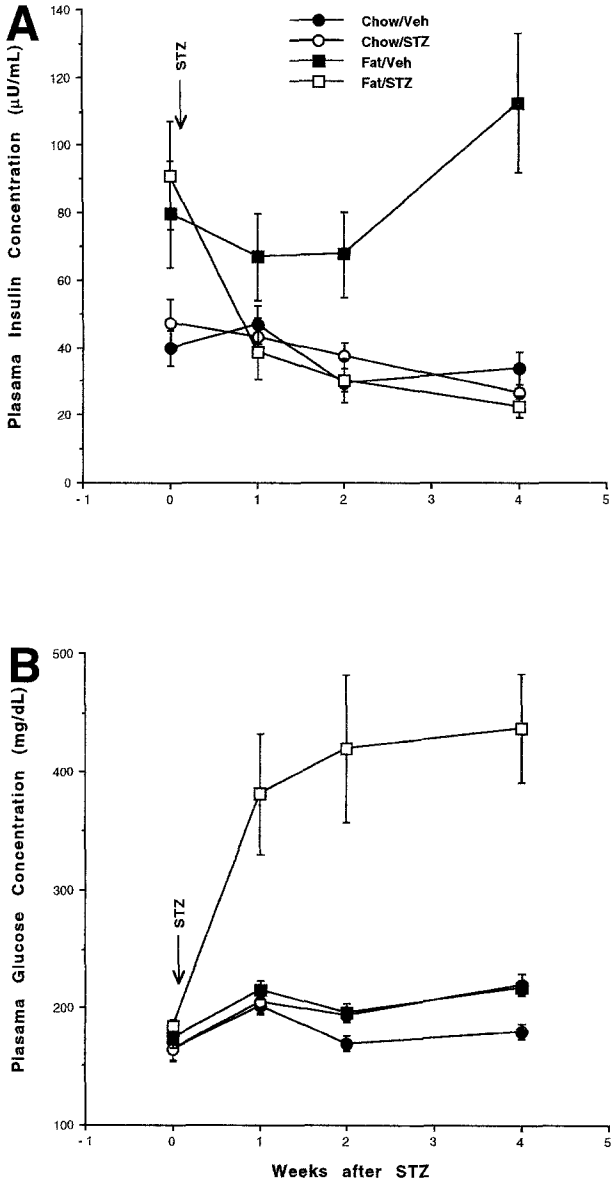

Fig 2. Plasma insulin (A) and glucose (B) before and after STZ injection in ICR mice. Mice were fed chow or fat-enriched diets at 3 weeks of age, and plasma glucose concentrations measured 3 weeks later. They were then injected with STZ (time 0) and maintained on the same diets. Plasma glucose concentrations measured 1, 2, and 4 weeks later.

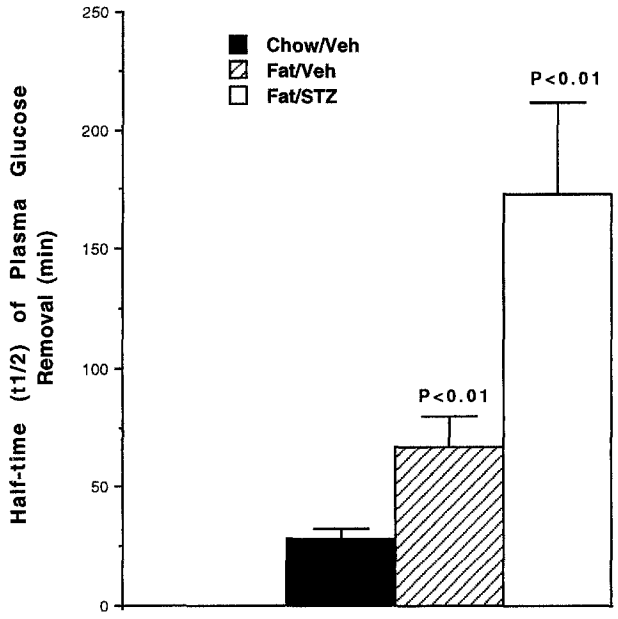

Fig 3. The $t_{1/2}$ of removal of glucose from plasma in 3 groups of ICR mice before and after IV injection of insulin (0.1 U/kg body weight).

the treatment of NIDDM, we evaluated the ability of drugs commonly used to treat NIDDM to decrease glucose levels in three of these diabetic mouse models (Fig 5). These results indicate that both metformin and tolbutamide decrease plasma glucose significantly in hyperglycemic fat-fed or fructose-fed C57BL/6J mice, as well as fat-fed ICR mice.

DISCUSSION

The current study was based on the hypothesis that mice fed either a high-fat or high-fructose diet would become insulin-resistant and hyperinsulinemic, and that hyperglycemia would occur when they were injected with a dose of STZ that would have little or no effect on plasma glucose concentrations in chow-fed mice. Before discussing the results of this study in light of our experimental goals, it is necessary both to acknowledge the work of others who have used STZ in an effort to develop an experimental model of NIDDM and to define the difference between our approach and theirs. In previous studies, STZ was given to neonatal rats on either the day of birth or 2 or 5 days later.[12-14] The first detectable metabolic defect in neonatal rats is a decrease in circulating insulin concentrations, with hyperglycemia developing during maturation when the subnormal insulin concentrations can no longer maintain glucose homeostasis. This model is in marked contrast to the one we have described in this report in which insulin resistance and hyperinsulinemia precede the development of hyperglycemia. Indeed, it is obvious from the results in Table 2 and Fig 1 that the circulating insulin concentrations are at least as high in fat-fed or fructose-fed mice following STZ injection as in chow-fed control animals. In other words, neonatal rats are hyperglycemic in the presence of hypoinsulinemia, whereas hyperglycemia develops following STZ injection in fructose-fed and fat-fed mice despite insulin concentrations that are equal to or higher than the control values. The two approaches result in very disparate animal models of NIDDM. Which model is "better" can be debated, and this decision would depend to a large extent on the goal of the investigator. On the other hand, we would submit that the natural history of NIDDM as defined by prospective studies[6,7] is more closely simulated by the mouse models we have described.

If we now focus on our results, the results presented provide evidence for both of these premises. In terms of insulin resistance, the data in Figs 1 and 2 and Table 2 show that plasma insulin concentrations increased in both strains of mice when they were fed diets enriched in either fat or fructose. In the absence of a decrease in plasma glucose, hyperinsulinemia provides presumptive evidence for the presence of insulin resistance. The results shown in Figs 3 and 4 provide direct evidence of resistance to insulin-mediated glucose disposal in

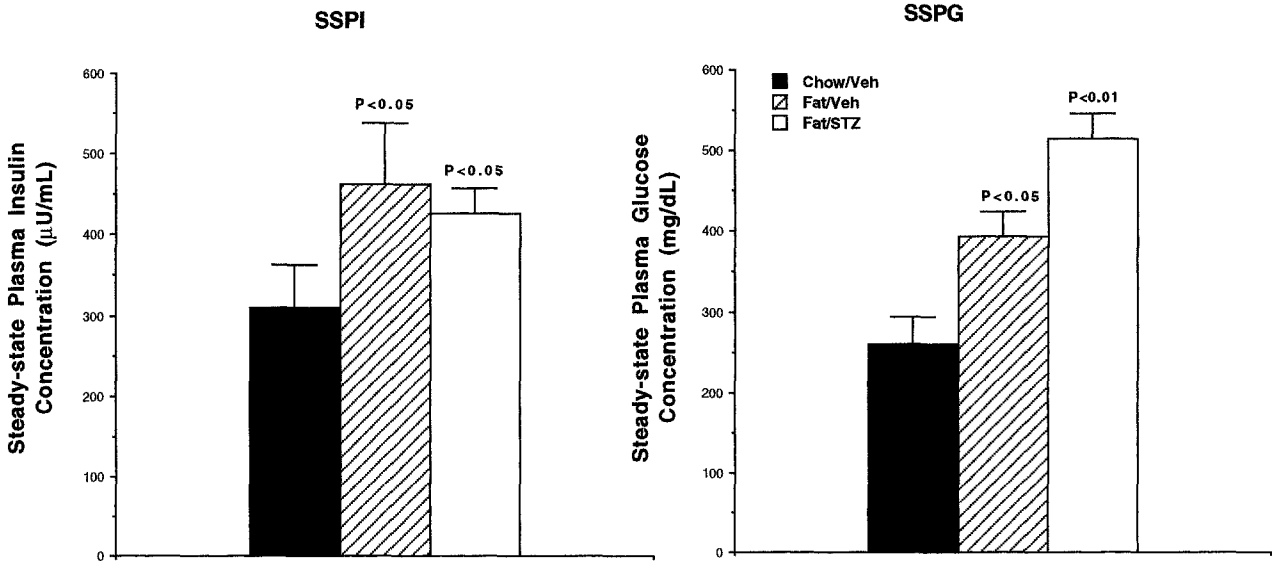

Fig 4. SSPI and SSPG concentrations during the last 40 minutes of a 135-minute infusion of insulin and glucose.

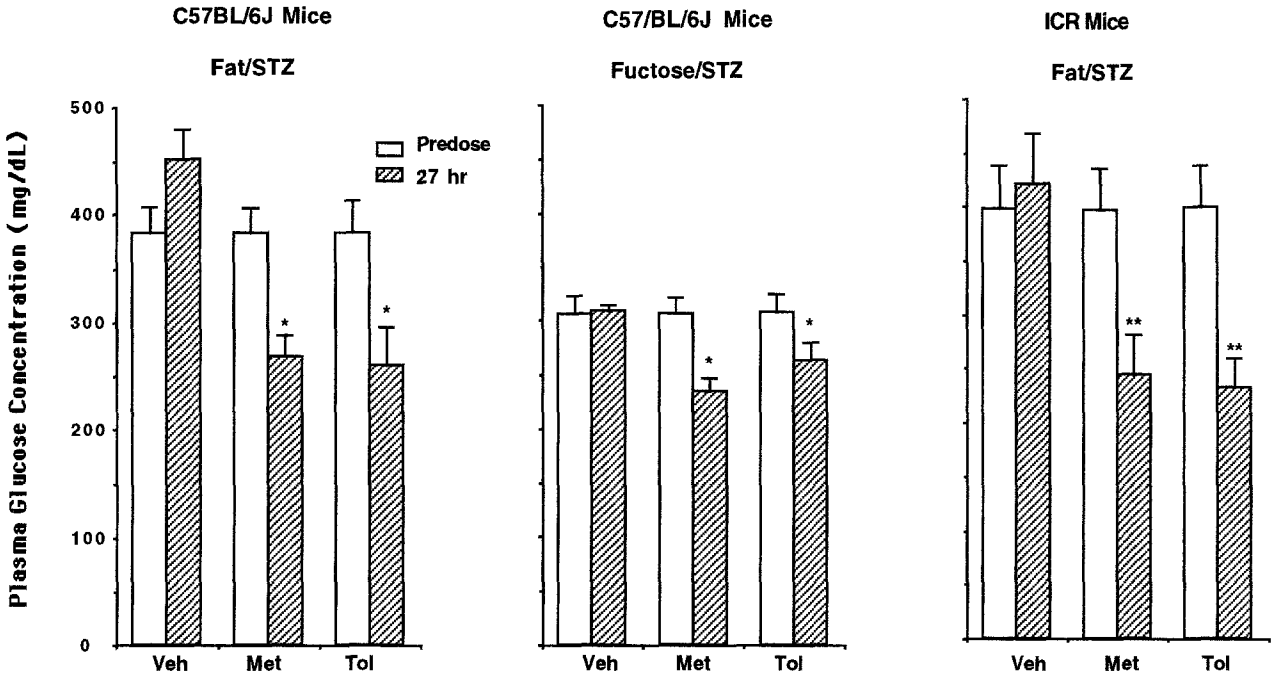

Fig 5. Plasma glucose concentrations following oral administration of vehicle, metformin, or tolbutamide in 3 mouse models of NIDDM. Mice were treated at 0, 8, and 24 hours, and plasma glucose concentrations measured at 0 hours (predose) and 27 hours (3 hours after the third dose).

ICR mice fed a fat-enriched diet. These results also indicate that physiological studies can be performed in these mouse models.

Although the dietary effects were similar in general in the two strains of mice, there were differences that deserve comment. Focusing on the C57BL/6J mouse, it appears from Table 2 that the high-fat diet resulted in a much greater increase in plasma insulin in vehicle-injected mice, and presumably more insulin resistance, than in chow-fed or fructose-fed mice. The higher insulin concentrations in fat-fed mice before STZ injection may have lengthened the time required for a decrease to an insulin concentration that was no longer sufficient to maintain euglycemia. As such, this might help explain (Fig 1) why hyperglycemia developed more slowly in fat-fed mice.

If we now turn to our second hypothesis, the results presented in Figs 1 and 2 also demonstrate that hyperglycemia develops in dietary-induced insulin-resistant mice injected with a dose of STZ that is not high enough to lead to an increase in glucose concentrations in mice fed conventional chow. Although this was true of both mouse strains, differences were also noted in this context. Fat-fed ICR mice appear to be more susceptible to STZ injection than fat-fed C57BL/6J mice. Specifically, in comparing Figs 1 and 2, ICR mice developed hyperglycemia more rapidly and had a higher mean glucose concentration 4 weeks after STZ than the corresponding C57BL/6J mice fed the same diet. The observation that ICR mice seemed more susceptible to the effects of STZ was somewhat surprising, given the evidence that the C57BL/6J mouse is the background strain for the ob/ob mutation and contains genes that render it susceptible to fat-induced diabetes.[15-17] Indeed, it has been shown that frank hyperglycemia will develop in C57BL/6J mice fed high-fat diets[15] and/or high-fat/high–simple-carbohydrate diets[17] for 5 to 6 months. However, these mice are also frankly hyperinsulinemic when they develop diabetes, and in this sense, they have different metabolic characteristics than the models described herein. Another obvious difference is that hyperglycemia develops much more rapidly in STZ-injected mice preconditioned with either a fat- or fructose-enriched diet.

Given the observations that both diet and mouse strain are variables for the diabetogenic effects of STZ in mice, the issue to address at this point is how these data can be used to accomplish the goal of the study, ie, identification of a mouse model to use in studying the pathophysiology of NIDDM. In this context, we believe that the ideal model should satisfy the following two criteria: (1) the metabolic characteristics are similar to those of patients with NIDDM, and (2) neither availability nor cost should be a burden. Based on the results presented, it appears that STZ-injected fat-fed and fructose-fed C57BL/6J mice and fat-fed ICR mice satisfy the first criterion. All three models became hyperinsulinemic, and presumably insulin-resistant, in response to the special diets but did not develop diabetes until injected with STZ. As such, they simulate the metabolic characteristics of individuals at increased risk to develop NIDDM because of insulin resistance.[1,3-7] When their capacity to maintain the degree of hyperinsulinemia required to overcome the insulin resistance caused by dietary manipulations is compromised by injection of STZ, the decrease in the insulin concentration to a value equal to that of chow-fed mice renders them incapable of maintaining glucose homeostasis. In other words, similar to the situation in hyperglycemic patients with NIDDM,[9] they have insulin concentrations equal in absolute terms to those of the nondiabetic control group but not high enough to overcome the insulin resistance—these mice are phenotypically very similar to patients with NIDDM. Finally, the fact that both metformin and tolbutamide were capable of significantly decreasing plasma glucose in these rodent models

of NIDDM further attests to their similarity to patients with NIDDM.

As to the second criterion, it is obvious that the use of STZ-injected fat-fed and fructose-fed C57BL/6J or fat-fed ICR mice as a model of NIDDM is cost-effective relative to the use of either db/db or ob/ob mice. Additionally, either strain can be readily obtained from most animal suppliers, in contrast to db/db or ob/ob mice. Since the data presented indicate that both of these models closely simulated the metabolic characteristic of patients with NIDDM, their use seems to offer significant advantages to the investigator.

Implicit in this study was the view that administration of a given amount of STZ will lead to the loss of a given amount of β-cell mass and render the STZ-treated mouse susceptible to develop hyperglycemia. Obviously, the situation is more complicated. For example, fat-fed mice had higher glucose concentrations than their chow-fed controls, which could have rendered them more susceptible to the effects of STZ. However, this was not the case in fructose-fed mice, and differences in basal glucose could not account for the enhanced diabetogenic effects in fructose-fed mice. Furthermore, in the case of fat-fed mice, it was obviously insulin resistance that led to the modest increase in glucose associated with the enhanced susceptibility to the diabetogenic effect of STZ. It is also clear that the strain of the mouse model will play a role in the modulation of both the metabolic response to the diets enriched in fat or fructose and the response to STZ. Indeed, it was exactly for this reason that we used both an outbred (ICR) and an inbred (C57BL/6J) strain for these experiments. Not surprisingly, the specific findings in the two strains were different. However, and more importantly, the results were qualitatively similar. Specifically, we demonstrated that both species developed insulin resistance and compensatory hyperinsulinemia when fed diets enriched with either fat or fructose, and that hyperglycemia developed in fat-fed and fructose-fed mice of both strains in response to amounts of STZ that did not increase glucose concentrations in chow-fed mice.

In conclusion, feeding C57BL/6J and ICR mice with diets high in fat or fructose leads to insulin resistance and hyperinsulinemia. Hyperglycemia develops in these mice when they are injected with a dose of STZ that does not cause hyperglycemia in chow-fed animals of the same strain. ICR mice seem more susceptible to the effect of both the high-fat diet and STZ. The metabolic characteristics of fat-fed STZ-injected ICR mice bear a striking resemblance to those of patients with NIDDM, providing an easily accessible and inexpensive substitute for the mice conventionally used to study NIDDM.

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