Effect of Nicotinic Acid–induced Insulin Resistance on Pancreatic B Cell Function in Normal and Streptozocin-treated Baboons

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Abstract

To study the interaction between insulin secretion and insulin action in maintaining glucose homeostasis, we induced experimental insulin resistance in eight normal baboons, in six baboons treated with 40 mg/kg streptozocin (STZ-40), and in six baboons treated with 200 mg/kg streptozocin (STZ-200). Insulin resistance was induced by a 20-d continuous intravenous infusion of nicotinic acid (NA). Normal animals showed compensatory increases in several measures of insulin secretion (fasting insulin [FI], acute insulin response to arginine [AIR$_{arg}$], acute insulin response to glucose [AIR$_{gluc}$], and glucose potentiation slope [ΔAIR$_{arg}$/ΔG]), with no net change in fasting plasma glucose (FPG) or glycosylated hemoglobin (HbA$_{1c}$). STZ-40 animals showed compensatory increases in FI, AIR$_{arg}$, and AIR$_{gluc}$, but ΔAIR$_{arg}$/ΔG failed to compensate. Although FPG remained normal in this group during NA infusion, HbA$_{1c}$ rose significantly. STZ-200 animals failed to show compensatory changes in both AIR$_{gluc}$ and ΔAIR$_{arg}$/ΔG, with both HbA$_{1c}$ and FPG rising. These animals showed a paradoxical inhibition of insulin secretion in response to intravenous glucose during NA infusion, at a time when they were hyperglycemic. These data indicate that a significant degree of insulin resistance does not cause hyperglycemia in the presence of normal B cell function but, in animals with reduced B cell mass and superimposed insulin resistance, the degree of hyperglycemia is proportional to the degree of pancreatic B cell dysfunction. (*J. Clin. Invest.* 1991. 87:1395–1401.) Key words: nicotinic acid • insulin resistance • streptozocin • B cell dysfunction • hyperglycemia • baboon

Introduction

Investigation of the interaction between insulin secretion and insulin action in maintaining glucose homeostasis is fundamental to understanding the pathophysiology of many types of diabetes mellitus. Non–insulin-dependent diabetes (NIDDM)[1] is a heterogenous disorder involving defects in both insulin

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1. *Abbreviations used in this paper:* AIR$_{arg}$ and AIR$_{gluc}$, acute insulin response to arginine and glucose, respectively; ΔAIR$_{arg}$/ΔG, glucose potentiation slope of AIR$_{arg}$; FI, fasting insulin; HbA$_{1c}$, glycosylated hemoglobin; IDDM, insulin-dependent diabetes mellitus; NA, nicotinic acid; NIDDM, non–insulin-dependent diabetes mellitus; S$_I$, insulin sensitivity index; STZ, streptozocin.

secretion and insulin action (1). In insulin-dependent diabetes (IDDM) the acute presentation of hyperglycemia usually occurs when increased insulin resistance, intercurrent illness, or puberty are superimposed on subclinical B cell dysfunction.

We wished to test the hypothesis that, whereas normal pancreatic islets are able to adapt to periods of insulin resistance, those with B cell dysfunction may be unable to increase insulin secretion sufficiently to maintain normoglycemia. As a model for graded B cell dysfunction, we have used streptozocin (STZ)-treated adolescent baboons (2). We have previously shown that, at low doses of STZ, the changes in pancreatic B cell function in these animals are similar to those seen in nondiabetic first-degree relatives of IDDM patients during the preclinical period of IDDM (3, 4). We have also shown that higher doses of STZ induce clinical states of non–insulin-requiring or insulin-requiring diabetes, and that the degree of B cell dysfunction measured in vivo within 3 d of sacrifice correlates closely with the quantitative estimates of overall B cell mass and pancreatic insulin content measured in the same animals (5).

In determining whether normal or STZ-treated animals are capable of adapting to periods of insulin resistance, it is necessary to choose an agent that causes a reversible reduction in peripheral insulin action without having direct effects on the pancreatic B cell. Nicotinic acid (NA), the B group vitamin used in long-term treatment of some of the hyperlipidemic syndromes, fulfills these requirements. Acutely (within a few hours) NA lowers plasma free fatty acid levels (6–9) resulting in improved insulin action (10–12). However, during prolonged administration of NA (several days) free fatty acid levels are increased (13). Since the increased availability of free fatty acids markedly impairs glucose utilization in muscle and other tissues (14–16), this is the likely explanation for the insulin resistance associated with long-term NA treatment (17–21). Treatment of normal men with 2 wk of oral NA (up to 2 g/d) was associated with a twofold increase in basal and stimulated insulin levels and a profound reduction in insulin sensitivity (21). That these changes are not due to direct stimulation of the islets by NA has been shown both in perfusion studies of rat islets (22) and in pancreatic rat slices (23) where NA, even in high concentrations, both under basal conditions and during maximal stimulation by glucose, glucagon, or theophylline, did not enhance insulin secretion.

We have therefore determined the effect of prolonged NA infusion on insulin sensitivity, pancreatic B cell function, fasting, and postprandial glycemia in normal adolescent baboons and in those with STZ-induced subclinical B cell dysfunction.

Methods

Animals

These studies were carried out on conscious adolescent male baboons (Papio cyanocephalus/anubis), weighing 8–14 kg, which were adapted

to living in primate tethers. Silastic catheters, permanently implanted in the vena cava through either the jugular or femoral vein were kept patent by a continuous infusion of 150 mmol/liter NaCl and 5 U/ml heparin at the rate of 80–100 ml/24 h. At least 7 d of recovery time after catheter implantation were allowed before initiation of the studies. The catheters extended outside the cages, allowing frequent blood sampling as well as infusion of test substances without disturbing the animals. Except for the day of study, animals were fed two equal meals at 0800 and 1300 hours. The study was approved by the University of Washington Regional Primate Center's Experimental Studies Review Committee.

Materials

STZ and NA were obtained from Sigma Chemical Co., St. Louis, MO. NA was prepared as a 0.1% solution. Arginine hydrochloride was obtained from Cutter Laboratories, Sacramento, CA, prepared at a 10% solution. Somatostatin was obtained from Bachem Inc., Torrance, CA.

STZ treatment

STZ was given in the fasting state as an intravenous injection. A total of 10 animals were used as outlined in Table I. Six animals received a single dose of 40 mg/kg (STZ-40). Six animals received two additional doses of 80 mg/kg, separated by at least 1 wk, giving a cumulative dose of 200 mg/kg (STZ-200) for these animals. There were eight normal, six STZ-40, and six STZ-200 animals. There were no significant differences in weight among the groups. All experiments were performed at least 1 wk after the last dose of STZ.

NA treatment

NA was given as a continuous intravenous infusion at a dose of 60 mg/kg per d for 10 d followed by 120 mg/kg per d for a further 10 d. At each stage (normal, STZ-40, or STZ-200) animals had B cell function and insulin sensitivity measured within 3 d before commencing the NA infusion and again during the last 3 d of the higher-dose NA infusion.

B cell function tests

These tests were carried out after an 18-h overnight fast. Samples were drawn into tubes containing EDTA and Trasylol, placed on ice, and centrifuged within 10 min. Arginine stimulation, both at basal glucose and during hyperglycemic clamp, glucose stimulation, and measurement of insulin sensitivity were performed. All studies were carried out on a single day with glucose stimulation and insulin sensitivity measurements obtained between the basal arginine stimulation and the hyperglycemic clamp. Plasma was then frozen until assayed for immunoreactive insulin. At the end of the study, the red cells were resuspended in 150 mmol/liter NaCl and reinfused into the animal.

Table I. Explanation of Which Animals Were Studied at Each Stage

Animal no.	Normal	STZ-40	STZ-200
1	+	−	−
2	+	+	+
3	+	−	−
4	+	+	+
5	+	+	+
6	+	+	+
7	+	−	+
8	+	−	+
9	−	+	−
10	−	+	−
Total	8	6	6

Symbols: +, the animal was studied at this stage; −, the animal was not studied at this stage.

Arginine stimulation. Insulin secretory responses to intravenous arginine were measured at two different plasma glucose levels. At each level three prestimulus blood samples were obtained 10 min, 5 min, and immediately before administration of arginine. A dose of 0.07 g/kg 10% arginine hydrochloride was administered intravenously in 30 s, the beginning of which was designated time zero. Blood samples were obtained 2, 3, 4, and 5 min after arginine administration. 3 h later (after the intravenous glucose tolerance test; see below) a variable rate infusion of 50% dextrose was delivered by a syringe pump (model 355, Sage Instruments, Cambridge, MA) in order to raise and maintain the plasma glucose level at ∼ 14.0 mmol/liter. Blood samples (0.5 ml) were obtained every 3–5 min for plasma glucose measurement, and based on these values the glucose infusion rate was adjusted. 40 min after commencing the hyperglycemic clamp, a second arginine pulse (0.07 g/kg) was given, and the insulin response was measured as before.

Insulin sensitivity testing. A modified intravenous glucose tolerance test was performed. Blood samples were obtained 10, 5, and 2 min before glucose injection. Immediately after this sample was taken, an intravenous bolus of 200 μg somatostatin was given, followed at time zero by a bolus of 0.3 g/kg 50% dextrose. Further blood samples were obtained 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min after glucose injection. From the glucose and insulin data an index of tissue insulin sensitivity (S_I) was calculated using the minimal modeling technique of Bergman et al. (24). This modification with somatostatin has been shown to improve parameter identification and thereby increase the precision of the S_I measurement (25). S_I was measured in all normal and STZ-40 animals before and during the last 3 d of NA infusion. S_I could not be measured in STZ-200 animals because there was insufficient insulin response to allow accurate modeling.

Glucose stimulation. An intravenous glucose tolerance test was performed. Blood samples were obtained 10 min, 5 min, and immediately before glucose injection. A bolus of 0.3 g/kg 50% dextrose was given in 30 s commencing at time zero. Further blood samples were obtained 2, 3, 4, 5, 6, 8, and 10 min after beginning the dextrose injection.

Analytical methods. Plasma insulin was assayed by a modification of the double-antibody method of Morgan and Lazarow (26). Plasma glucose was measured using a glucose analyzer (Beckman Instruments, Inc., Palo Alto, CA). All samples from an individual study were analyzed in duplicate in a single assay. Glycosylated hemoglobin (HbA_{1c}) was measured using a sensitive calorimetric thiobarbituric acid method (27).

Calculations and statistical analysis. Fasting plasma glucose and insulin were calculated as the mean of the three samples before the first arginine injection. The acute insulin response to glucose (AIR_{gluc}) was calculated as the mean of the poststimulus samples obtained at 2, 3, 4, 5, 6, 8, and 10 min after the intravenous glucose injection minus the mean of the three prestimulus samples. The acute insulin response to arginine at fasting plasma glucose (AIR_{arg}) was calculated as the mean of the poststimulus samples obtained at 2, 3, 4, and 5 min minus the mean of the three prestimulus samples.

Since the AIR_{arg} increases in a linear manner in the range of plasma glucose from 5.56–16.7 mmol/liter (28), we calculated the slope of the increase in the AIR_{arg} as follows: $(AIR_{arg}h − AIR_{arg}l)/\Delta$ plasma glucose, where $AIR_{arg}h$ is the acute insulin response to arginine at the higher glucose level, $AIR_{arg}l$ is the same calculation at the lower glucose level, and Δ plasma glucose is the difference between the two glucose levels.

Nonparametric statistics were used throughout using the Statview II program (Abacus Concepts, Inc., Berkeley, CA) on a Macintosh SE/30 computer. Comparison between any two groups (e.g., normals before NA vs. STZ-40 before NA) was tested using the Mann-Whitney U-test; for all three groups the Kruskal-Wallis one-way analysis of variance was employed. For changes within each group (before and during NA treatment), the Wilcoxon signed rank test was used.

Results

Insulin sensitivity. S_I fell in all animals during NA infusion (Fig. 1); S_I for normal animals before NA was $4.0\pm0.8 \times 10^5$
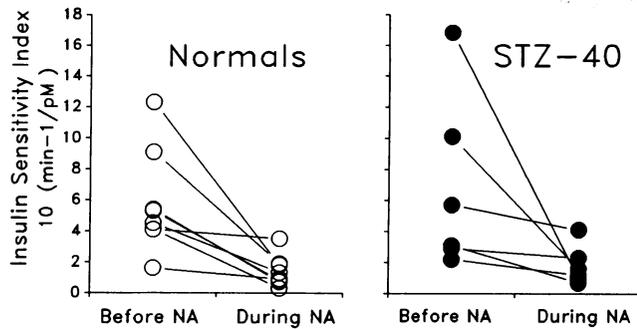
Figure 1. Changes in insulin sensitivity index before and during NA infusion in normal (o) and STZ-40 (•) animals.

(min⁻¹/pM) and fell to $1.0\pm0.2 \times 10^5$ (min⁻¹/pM), $P < 0.01$. For STZ-40 animals, S_I before NA infusion was $4.6\pm1.6 \times 10^5$ (min⁻¹/pM), not statistically different from normals. During NA infusion S_I fell to $1.3\pm0.5 \times 10^5$ (min⁻¹/pM), $P < 0.03$, in STZ-40 animals indicating that a similar degree of insulin resistance was induced in both groups.

Pancreatic B cell function. In the normal animals treated with NA, fasting insulin (FI) increased about twofold (Table II). AIR_{arg} at basal glucose increased from 880 ± 190 to $1,730\pm488$ pM ($P < 0.07$) (Fig. 2, *left, upper panel*) and also during hyperglycemia clamp of ~ 14 mM, from $2,769\pm582$ to $5,106\pm1044$ pM ($P < 0.03$), as illustrated in Fig. 3, *top panel.* The slope of glucose potentiation of AIR_{arg} ($\Delta AIR_{arg}/\Delta G$) therefore increased from 191 ± 41 to 361 ± 85 pM$_{ins} \cdot$ mM$_{gluc}^{-1}$, $P < 0.05$, (Table II and Fig. 3, *upper panel*). AIR_{gluc} in the normal animals increased from 902 ± 108 to $1,703\pm408$ pM during NA infusion ($P < 0.04$) (Table II and Fig. 2, *right, upper panel*).

In the STZ-40 animals all of the measures of B cell function before NA infusion were reduced by about a third but none were significantly different from those of the normal animals before NA infusion. During NA infusion, fasting insulin and AIR_{arg} at basal glucose increased significantly (Table II and Fig. 2, *left, middle panel*). However, AIR_{arg} during hyperglycemic clamp failed to show a compensatory increase during NA infusion (Fig. 3, *middle panel*), such that $\Delta AIR_{arg}/\Delta G$ remained unchanged (Table II). AIR_{gluc} did show a compensatory in-

crease in STZ-40 animals from 602 ± 143 to $1,173\pm322$, $P < 0.05$, (Table II and Fig. 2, *right, middle panel*). The changes in AIR_{gluc} and $\Delta AIR_{arg}/\Delta G$ during NA-induced insulin resistance are further illustrated in Fig. 4, for normal and STZ-40 animals. S_I, AIR_{gluc}, and $\Delta AIR_{arg}/\Delta G$ have been obtained in a group of 29 normal animals. These animals spanned a wide range of S_I (seven had S_I of < 1.0, five had S_I of 1.0–1.9, six had S_I of 2.0–2.9, four had S_I of 3.0–4.9, three had S_I of 5.0–7.9, and four had S_I of 8.0–12.9). There is a significant inverse correlation between S_I and AIR_{gluc} such that ln $AIR_{gluc} = 5.09$–0.37 ln S_I, $r = 0.56$, $P < 0.001$. A similar relationship exists between S_I and $\Delta AIR_{arg}/\Delta G$ (ln $\Delta AIR_{arg}/\Delta G = 5.47$–0.46 ln S_I, $r = 0.66$, $P < 0.001$). In Fig. 4 the curved lines show the mean±1 SD for these normal animals and provide a setting in which to evaluate the changes seen in normal and STZ-40 animals during NA treatment. Both groups showed an appropriate increase in AIR_{gluc} as S_I fell, such that they remained within the expected normal range (*upper panel*, Fig. 4). However, although the normal animals showed an appropriate compensatory increase in $\Delta AIR_{arg}/\Delta G$ to the reduction in S_I, STZ-40 animals failed to do so, thereby falling outside the expected normal range (*lower panel*, Fig. 4).

The effects of STZ in reducing insulin secretion is evident over all three groups before NA, using the Kruskal-Wallis test. Reduction in AIR_{arg} ($P < 0.02$), AIR_{gluc} ($P < 0.002$), and $\Delta AIR_{arg}/\Delta G$ ($P < 0.002$) were highly significant. Comparing STZ-200 animals with normals using the Mann-Whitney U-test, the fasting insulin, AIR_{gluc}, AIR_{arg}, and $\Delta AIR_{arg}/\Delta G$ before NA were significantly lower than in normal animals before NA (Table II, $P < 0.05$). During NA infusion there were slight, but statistically insignificant increases in fasting insulin and AIR_{arg} (Table II and Fig. 2, *left, lower panel*). In contrast, AIR_{arg} during hyperglycemic clamp showed a slight but significant decrease during NA infusion from 360 ± 144 to 276 ± 132 pM ($P < 0.05$) such that $\Delta AIR_{arg}/\Delta G$ became negative (Table II, and Fig. 3, *lower panel*). After intravenous glucose there was also a paradoxical decrement in insulin secretion during NA infusion (Fig. 2, *right, lower panel*). In STZ-200 animals before NA, insulin rose from 96 ± 12 pM before intravenous glucose to remain elevated at ~ 200 pM from 2 to 6 min. In STZ-200 animals during NA, basal insulin was 168 ± 48 pM before glu-

Table II. Changes in Pancreatic B Cell Function before and during Nicotinic Acid Infusion in Normal, STZ-40, and STZ-200 Animals

	Normals (*n* = 8)		STZ-40 (*n* = 6)		STZ-200 (*n* = 6)	
	Before NA	During NA	Before NA	During NA	Before NA	During NA
Fasting insulin (*pM*)	257±55	NS 536±224	163±31	0.03 550±155	171±24	NS 230±41
AIR_{gluc} (*pM*)	902±108	0.04 1,703±408	602±143	0.05 1,173±322	100±25	0.03* −24±8
AIR_{arg} (*pM*)	880±190	0.07 1,730±488	695±164	0.05 1,659±284	238±81	NS 404±199
$\Delta AIR_{arg}/\Delta G$(pM$_{ins} \cdot$ mM$^{-1}_{gluc}$)	191±41	0.05 361±85	105±28	NS 84±30	15±7	0.03* −16±8

P value indicated using Wilcoxon signed rank test; * Significant decrease during NA.
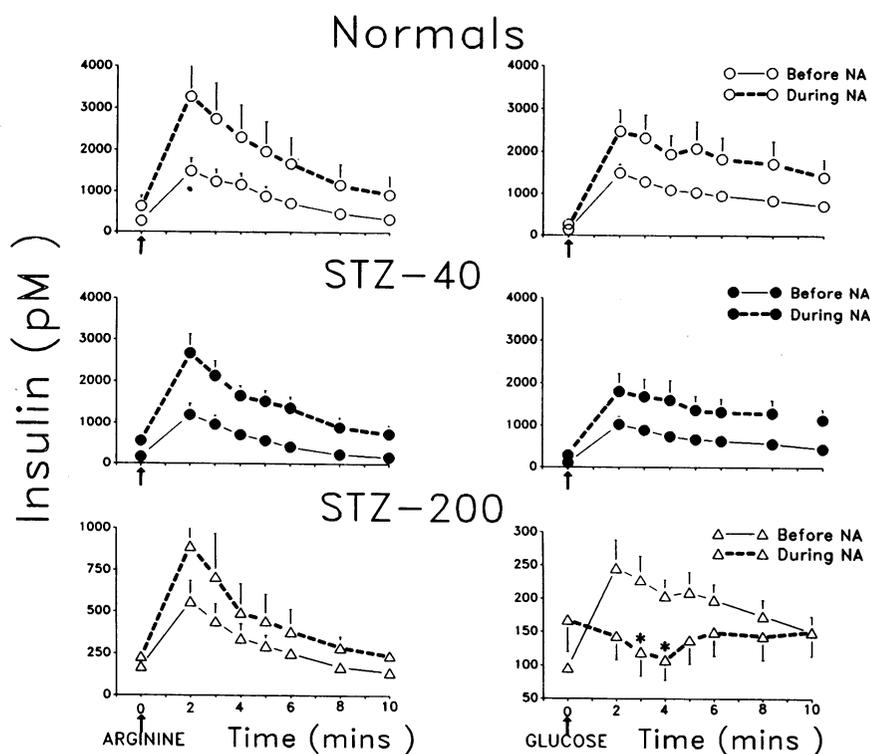
Figure 2. The acute insulin responses to arginine (left panels) and glucose (right panels) at basal glucose in normal animals before NA infusion (o——o), normal animals during NA infusion (o - - - o), upper panel; STZ-40 animals before NA infusion (●——●), STZ-40 animals during NA infusion (● - - - ●), middle panel; STZ-200 animals before NA infusion (△——△), and STZ-200 animals during NA infusion (△ - - - △), lower panel.

cose, not significantly higher than the basal insulin before NA, but fell to a nadir of 108 ± 30 pM at 4 min ($P < 0.05$) before returning to 150 ± 36 pM at 10 min.

Glucose homeostasis. The combined effects of insulin resistance and pancreatic B cell dysfunction on fasting plasma glucose and postprandial glycemia (as assessed by HbA_{1c}) are shown in Fig. 5. For normal animals FPG remained ~ 5 mM
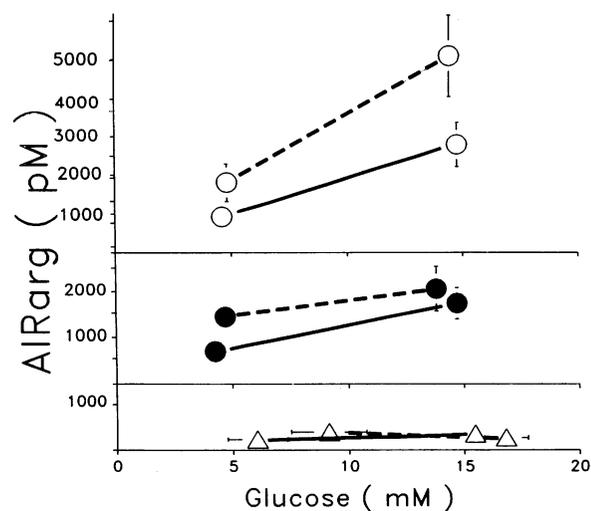
Figure 3. AIR_{arg} at two different blood glucose levels in normal animals before NA infusion (o——o), normal animals during NA infusion (o - - - o), upper panel; STZ-40 animals before NA infusion (●——●), STZ-40 animals during NA infusion (● - - - ●), middle panel; STZ-200 animals before NA infusion (△——△), and STZ-200 animals during NA infusion (△ - - - △), lower panel.
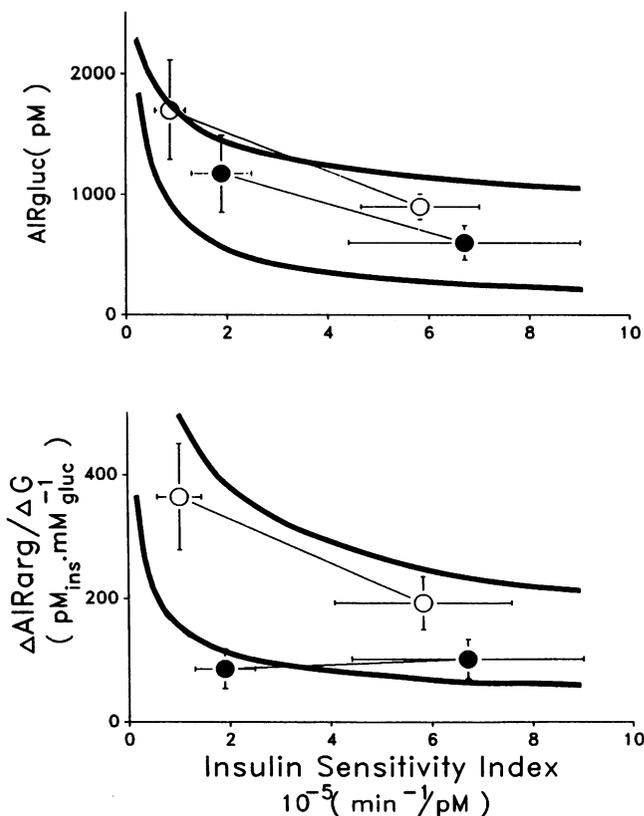
Figure 4. Changes in AIR_{gluc} (upper panel) and $\Delta AIR_{arg}/\Delta G$ (lower panel) in response to a drop in insulin sensitivity in normal animals (o——o) and STZ-40 animals (●——●). The normal range (mean±1 SD) for these relationships is indicated by the curved lines (determined from 29 normal baboons).

before, during, and after NA infusion. HbA_{1c} was $7.1\pm0.5\%$ before NA and showed no significant change during NA treatment (Fig. 5, *lower panel*). For STZ-40 animals FPG remained ~ 5 mM before, during, and after NA infusion. HbA_{1c} rose steadily, however, from $6.5\pm0.3\%$ before NA to $7.7\pm0.4\%$ at 15 d and 8.1 ± 0.5 at 20 d, values significantly higher than baseline ($P < 0.05$, Fig. 5, *lower panel*). Changes in STZ-200 animals were more striking. FPG rose from 4.9 ± 0.1 mM before NA to a plateau of ~ 9 mM from day 8 until the NA infusion was discontinued at 20 d ($P < 0.005$). 4 d after stopping NA the FPG had returned to a value of 4.8 ± 0.4 mM, no different from normal and STZ-40 animals (Fig. 5, *upper panel*). HbA_{1c} before NA was $6.6\pm0.6\%$ but rose steadily to a value of $8.4\pm0.6\%$ at 10 d, $10.3\pm1.0\%$ at 15 d, and $11.8\pm1.2\%$ at 20 d of NA infusion ($P < 0.01$, Fig. 5, *lower panel*).

Discussion

Since prolonged treatment with NA induces insulin resistance by an action on peripheral tissue (13–16) and does not affect B cells directly (22, 23), we have been able to examine the effects of superimposed insulin resistance on B cell adaptation and glucose homeostasis in the presence of normal and abnormal B cell function. In vivo insulin sensitivity can be measured either by euglycemic hyperinsulinemic clamp techniques or by frequently sampled modified intravenous glucose tolerance tests

Figure 5. Changes in fasting plasma glucose (*upper panel*) and HbA_{1c} (*lower panel*) before, during, and after 20 d of continuous intravenous infusion of NA in normal (o), STZ-40 (●) and STZ-200 (△) animals.

and computer modeling. These two techniques have been compared extensively in the past decade both in dogs (29) and in humans (30, 31). It is now clearly established that there is a wide range in insulin sensitivity between normal individuals using either methodology, that the correlation between the methods is excellent (29–31), and that, when corrections are made so that S_I measurements can be expressed in the same units, then S_I (by clamp) and S_I (by intravenous glucose tolerance test) give equivalent results (31). We chose to use the minimal model using an intravenous glucose tolerance test modified with somatostatin since this markedly improves the precision of the measurement (25) and allows measurement of insulin secretion and insulin sensitivity on the same day. We have shown previously, both in normal humans (3) and baboons (2), that there is an inverse correlation between insulin secretion and insulin sensitivity such that changes in either one can only be fully appreciated when considered in relation to the other (3, 4). The baboons in this study showed a profound reduction in insulin sensitivity after 2–3 wk of NA treatment comparable to that seen in human adults (21). Fasting and stimulated insulin levels increased two- to threefold to compensate for the insulin resistance, but stayed within the normal range for animals of that degree of insulin sensitivity (Fig. 4).

We have shown previously in baboons that there is a greater reduction in $\Delta AIR_{arg}/\Delta G$ than AIR_{gluc} or AIR_{arg} after STZ treatment (2). This suggests that there is differential sensitivity among these B cell function tests such that $\Delta AIR_{arg}/\Delta G$ might decline earlier than AIR_{gluc}, which in turn might decline earlier than AIR_{arg}. Ganda et al. (32) also found differential sensitivity among B cell function tests in human patients with "early" type I diabetes, finding that AIR_{gluc} declined earlier than AIR_{arg}. In the present study the STZ-40 animals before NA treatment had B cell function which was indistinguishable from the normal animals before NA treatment. During NA infusion their degree of increase in FI, AIR_{arg}, and AIR_{gluc} were very similar to normals during NA infusion. The only B cell function test which failed to compensate was $\Delta AIR_{arg}/\Delta G$, suggesting again that this is a very early indicator of B cell dysfunction.

In the STZ-200 animals B cell function before NA treatment was significantly impaired compared with normal animals before NA. During NA infusion there was a more pronounced failure of compensatory adaptation with no significant increase in FI or AIR_{arg}, and even a paradoxical decrease in both $\Delta AIR_{arg}/\Delta G$ and AIR_{gluc}.

The significance of these compensatory adaptations in B cell function in the presence of insulin resistance can be seen when examining the glycemic responses in these animals. We assessed both fasting plasma glucose and postprandial glycemia (as reflected by HbA_{1c}) during 20 d of NA treatment. In general fasting glucose levels are lower in baboons than in humans (2, 33). Nonenzymatic glycosylation of hemoglobin in mammals is determined by three major variables: mean plasma glucose concentration, red cell life span and red cell permeability (33). Since baboons have a higher red cell permeability than humans (33), and a red cell life span of 45 d compared with 120 d for human (34), it is possible to see changes in HbA_{1c} much earlier in baboons than in humans. In our normal animals, who had normal compensatory increases in both $\Delta AIR_{arg}/\Delta G$ and AIR_{gluc} in response to insulin resistance, fasting glucose and HbA_{1c} remained normal throughout NA treatment. This sug-

gests that B cell adaptation is complete in these animals and that even insulin resistance of this severity is not sufficient to cause hyperglycemia in the presence of normal B cell function. In STZ-40 animals where AIR_{gluc} adaptation was intact but $\Delta AIR_{arg}/\Delta G$ adaptation was markedly impaired, fasting plasma glucose was still maintained during NA treatment but HbA_{1c} rose suggesting postprandial hyperglycemia. This suggests that the physiological importance of the glucose potentiation slope ($\Delta AIR_{arg}/\Delta G$) is to enhance insulin secretion postprandially when not only glucose but amino acids and other substrate secretagogues are raised in the blood perfusing the islets. Streptozocin treatment causes a reduction in overall B cell mass (5), reducing overall secretory capacity such that the postprandial response is inadequate and glucose levels remain high. The STZ-200 animals had a more severe B cell lesion as evidenced by inadequate adaptive changes of both $\Delta AIR_{arg}/\Delta G$ and AIR_{gluc}. These animals developed overt diabetes, during the period of induced insulin resistance, which resolved after NA treatment was discontinued (Fig. 5). These data therefore suggest that, in the presence of significant insulin resistance, the degree of hyperglycemia which develops is proportional to the degree of B cell dysfunction and the ability to compensate for increased demand. Pascoe and Storlein (35) have recently shown that in STZ-treated rats, hyperglycemia only developed when insulin resistance (induced by eating a high fat diet) was superimposed on B-cell dysfunction.

One last finding is worthy of comment. It has been suggested that hyperglycemia itself impairs B cell function (36), and a paradoxical inhibition of insulin secretion after intravenous administration of glucose has been observed in some humans with NIDDM (37–39). Our data from STZ-200 animals during NA infusion support this concept. While normoglycemic, these animals showed an increase in insulin secretion after intravenous glucose, but when NA-induced insulin resistance and inadequate B cell adaptation resulted in hyperglycemia (Fig. 5), insulin secretion after intravenous glucose actually declined. In our study the nadir occurred at 4 min and had returned to basal by 10 min. Metz et al. (39) using a similar protocol in normal humans and patients with NIDDM found the nadir at 5–10 min with return to baseline by 15 min. These data, and those of our study therefore suggest that, in the presence of a B cell lesion, hyperglycemia exacerbates the degree of B cell dysfunction.

In summary, the present findings demonstrate clearly the relative contributions of pancreatic B cell dysfunction and peripheral insulin resistance to the development of hyperglycemia and show that hyperglycemia itself can further impair B cell function. These data therefore improve understanding of several clinical situations in both NIDDM and IDDM. In NIDDM significant improvements in both insulin action and insulin secretion have been induced by weight reduction or when hyperglycemia is reduced by insulin therapy (39–43). These improvements are maintained for 2 wk after withdrawal of insulin therapy (42).

The acute presentation of IDDM is often due to an intercurrent event which causes insulin resistance to develop in someone with subclinical B cell dysfunction. Because B cell compensation is incomplete, hyperglycemia develops. Insulin therapy may improve the situation in several ways. Exogenous insulin treatment may "rest" the remaining B cells, which may make them less vulnerable to further autoimmune destruction

and allow them to recover (44). Another mechanism by which improved glycemia may occur during the honeymoon period could be because insulin treatment improves insulin sensitivity (45, 46).

Our data also have implications for the treatment of individuals during the preclinical period of IDDM. Various agents have been suggested for the prevention of IDDM (47). Some of these, like corticosteroids, not only cause decreased insulin sensitivity, but also directly inhibit B cell function (48–50). Cyclosporine has been shown, in dogs, to cause an inhibition of insulin secretion which does not reverse completely on stopping the drug (51). A study of cyclosporine treatment in humans with multiple sclerosis showed no effect on glucose homeostasis and insulin secretion after 1 yr (52). However, such subjects would be expected to have normal pancreatic B cell function. First-degree relatives of type I diabetics under consideration for treatment to prevent clinical IDDM will have some degree of B cell dysfunction before treatment is started. It is unknown whether the use of corticosteroids, azathioprine, cyclosporine or other immunosuppressive agents will have a deleterious effect on B cell function or insulin sensitivity in these subjects. Our data on STZ-treated nonhuman primates suggests that this may well be a useful animal model in which to evaluate proposed immunosuppressive regimens for prevention of IDDM.

Acknowledgments

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