Glucose Modulation of Insulin and Glucagon Secretion in Nondiabetic and Diabetic Man

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SUMMARY

To ascertain whether the ability of glucose to influence the pancreatic islets response to a nonglucose stimulus is normal in type II diabetics, we have evaluated the modulating effect (Md) of the plasma glucose level (PG) on the acute insulin response (IRI) and glucagon response (IRG) to intravenous arginine in non-insulin-dependent diabetics (NIDDM) and nondiabetics (ND). Md_{IRI} or Md_{IRG} is the change in the hormonal response to arginine resulting from changes in plasma glucose level divided by the change in plasma glucose. Md has been determined over two ranges of PG: between normal fasting PG (level I) and mild hyperglycemia (~160 mg/dl, level II) and between mild hyperglycemia and marked hyperglycemia (~350 mg/dl, level III). Increases in PG augmented the IRI response in both groups, but the degree of augmentation was impaired in the NIDDM group. MD_{IRI} for ND and NIDDM between levels I and II were 20 ± 3 and 1.9 ± 0.6, respectively, and between levels II and III were 23 ± 5 and 2.3 ± 0.5, respectively ($P < 0.01$). Md_{IRI} correlated with fasting PG in ND and NIDDM. Changes in PG resulted in equivalent changes in the IRG response to arginine in both groups. Md_{IRG} for level I to II was −6.1 ± 1.0 and −6.0 ± 1.2, and for level II and III was −0.9 ± 0.4 and −1.2 ± 0.5 in ND and NIDDM, respectively. The impairment of MD_{IRI} and its relationship to fasting PG in NIDDM support the hypothesis that fasting hyperglycemia may be, in part, a compensatory mechanism for maintaining beta-cell response to nonglucose stimuli, thereby maintaining basal insulin levels. Md_{IRG} was normal in NIDDM when evaluated at comparable glucose levels in the ND and NIDDM groups. DIABETES 31:489–495, June 1982.

Ambient glucose concentration is known to affect pancreatic alpha- and beta-cell function in at least two important ways: (1) by directly stimulating and/or suppressing the secretion of insulin and glucagon and (2) by modulating the secretory responses of both types of islet cells to nonglucose secretogogues such as arginine, other amino acids, fatty acids, gastrointestinal hormones, and neurotransmitters.[1–8] In diabetes, the acute insulin response to glucose and the normal suppressive effect of glucose on glucagon secretion are both impaired whereas the responses of both types of islet cells to nonglucose secretogogues are retained.[7,9–15] Halter and co-workers have recently shown that the modulating effect of glucose on the acute insulin response to isoproterenol is impaired in non-insulin-dependent diabetes.[16] Whether the modulating effect of glucose on the alpha-cells' response to nonglucose secretogogues is impaired in diabetes has not been investigated.

Compared with nonobese nondiabetics, non-insulin-dependent diabetics have normal, or greater than normal, basal insulin levels and basal hyperglycemia.[17] Turner and Holman have hypothesized that in this form of diabetes the level of fasting plasma glucose is determined by the degree of elevation required to stimulate beta-cell secretion sufficiently to maintain their basal insulin concentration.[17] They argue that because of the anabolic functions of insulin involving carbohydrate, fat, and protein metabolism in multiple tissues, basal insulin is of primary importance to the organism. Others have claimed that basal insulin secretion is relatively independent of the direct stimulatory effect of the fasting plasma glucose concentration[18,19] and is controlled by a complex interplay of many nonglucose factors.[20] A modification of the hypothesis of Turner and Holman is that fasting plasma glucose maintains basal insulin by modulating the responsiveness of the beta-cells to nonglucose factors that directly control secretion rate. If the modulator effect of glucose is deficient in diabetes, an elevated fasting blood glucose concentration would be necessary to achieve a normal potentiation effect and consequently an adequate basal insulin level. Halter and co-workers found

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Received for publication 5 May 1981 and in revised form 1 February 1982.

this mechanism to be applicable for the isoproterenol-glucose interaction in their non-insulin-dependent diabetics.[16] The same mechanism, only reversed, might apply to the alpha-cell to account for the normal basal IRG usually found in diabetics.[7,13,14]

The present study was designed to (1) characterize and quantify the modulating effect of glucose on alpha- and beta-cell responsiveness to the nonglucose secretogogue arginine in nondiabetics, (2) examine whether the modulating effect of glucose on arginine-stimulated insulin and glucagon secretion is abnormal in NIDDM and, (3) to further investigate the hypothesis that compensatory hyperglycemia is NIDDM is a mechanism for maintenance of basal insulin levels.

MATERIALS AND METHODS

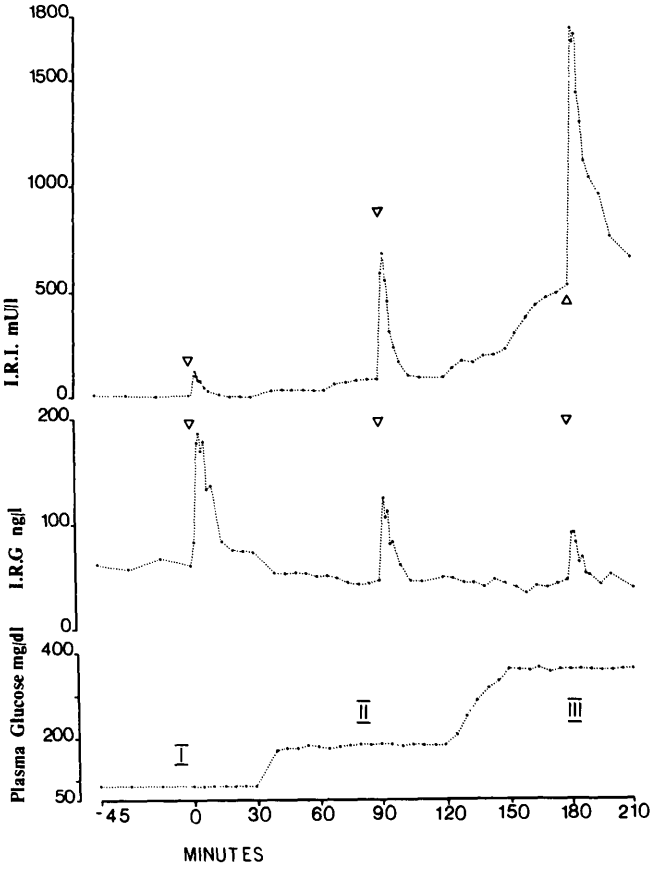
Subjects. Two groups of subjects were studied: 16 nondiabetics [age 27 ± 1 yr, % ideal body wt = 97.6 ± 0.8% (Metropolitan Life Insurance Tables, 1959), fasting plasma glucose 89 ± 3 mg/dl] and 7 non-insulin-dependent diabetics (age 40 ± 4 yr, % ideal body wt = 148.7 ± 5.0% and fasting plasma glucose 166 ± 14 mg/dl). All diabetics had fasting hyperglycemia (>150 mg/dl) at the time of the study or on at least one previous occasion. All nondiabetics were on an ad libitum diet. The NIDDM group had received standard diabetic dietary instruction. None of the volunteers had a chronic illness other than diabetes, and none were taking medications. The NIDDM group had never been treated with insulin or oral agents. All nondiabetics had a negative first-degree family history for diabetes. To assess the effect of the greater degree of obesity of the diabetics, a further control group (N = 5) was studied: obese nondiabetics (mean fasting plasma glucose 88 ± 2 mg/dl) who were of a similar age (40 ± 5 yr) and obesity (154.4 ± 6.7% ideal body wt) as the diabetics.

Protocol. All baseline studies were performed in the Seattle Public Health Hospital. Informed consent was obtained from all subjects before participation. After an overnight fast with the patient in a supine position, scalp vein needles were placed in the antecubital veins of both arms and were kept patent with a slow infusion of 0.9% saline. One of the lines was used for obtaining blood samples and the other line was used for infusing insulin, glucose, and arginine. In all experiments, baseline fasting blood samples were drawn at −45, −30, −15, and 0 min. At 0 time, arginine (5 g) was injected intravenously as a pulse over 15–20 s. Blood samples were obtained at 2, 3, 4, 5, 6, 8, 10, 15, and 30 min post-arginine injection.

Our protocol was designed to evaluate and compare the modulating effect of glucose on the alpha- and beta-cell response to arginine in nondiabetics and non-insulin-dependent diabetics at three different prestimulus glucose levels: glucose level I (average normal fasting plasma glucose for the nondiabetics), glucose level II (average fasting plasma glucose for the NIDDM group), and glucose level III (marked elevation of the plasma glucose over basal for both groups). To raise glucose levels, two methods of glucose infusion were used: a variable rate calculated to clamp glucose level at a desired level[21] and a standard rate of 1.5 g/min. The glucose infusions were begun 30 min after the first arginine pulse. In the nondiabetics, glucose levels were raised in two steps. In the first step, glucose concentrations were raised from natural fasting glucose (designated as glucose level I) to prestimulus glucose levels equivalent to the fasting plasma glucoses of the NIDDM group (designated as glucose level II) using the glucose clamp method to match nondiabetics with NIDDM. In the second step, glucose concentrations were raised from glucose level II to markedly elevated glucose levels (designated as glucose level III). To achieve glucose level III in the nondiabetics, the pump was run at maximum delivery rate giving an infusion rate of 1.5 g glucose/min. Glucose was administered according to each of these protocols for 1 h at which time the arginine pulse (5 g) was repeated as previously described with the glucose infusion continuing for an additional 30 min after the arginine pulse. All nondiabetics received the first step glucose increment and 9 of the 16 received the second step. The arginine pulse administered at each prestimulus glucose level is termed arginine pulse I, pulse II, and pulse III, respectively, to designate the respective glucose level at the time the arginine was administered. Figure 1 illustrates the above protocol in a representative nondiabetic. The ambient glucose levels of the NIDDM group were raised from glucose level II (their fasting) to glucose level III by the infusion of glucose at a rate of 1.5 g/min. They received two arginine pulses designated arginine pulse II and III. As a control for obesity in the NIDDM group, five obese nondiabetics received the same glucose infusion rate (1.5 g/min) and therefore had glucose level raised from level I to III.

Insulin was infused in the non-insulin-dependent diabet-

FIGURE 1. Acute insulin and acute glucagon responses to a 5-g pulse of arginine at glucose levels I, II, and III in a nondiabetic. Administration of arginine is indicated by the V.



ics to establish prestimulus glucose levels approximately equivalent to the fasting plasma glucose levels (glucose level I) in the nondiabetics. Five of the seven diabetics participated in the insulin infusion experiments. The first arginine pulse in this group of experiments is designated as arginine pulse II and was given at plasma glucose level II (fasting blood glucose for the NIDDM group). Thirty minutes after the administration of arginine, an intravenous infusion of monocomponent regular insulin (courtesy of Eli Lilly & Co, Indianapolis, Indiana) in 0.9% saline was started at a rate of 0.33 mU/kg/min. At the end of 1 h, the insulin was discontinued and a 30-min period was allowed to permit plasma insulin to return to basal levels.[16] Then another arginine pulse was administered and was designated as arginine pulse I since it was given at glucose level I.

Analytic methods. All blood samples in the study were venous plasma. When NIDDM were raised by a fixed glucose infusion rate from glucose level II to glucose level III, venous plasma samples were used.[16] For consistency, venous plasma levels in the nondiabetics were also used both during the variable glucose infusion and the fixed glucose infusion. All blood samples were heparinized, those for glucagon mixed with benzamidine at a final concentration of 0.05 M and kept on ice until separated by centrifugation. The plasma was frozen at −20°C until analyzed. Plasma insulin (IRI) and glucagon (IRG) were measured by radioimmunoassay[22,23] and plasma glucose by the glucose-oxidase technique (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, California).

Analysis of data. The acute insulin response (AIR) and the acute glucagon response (AGR) to arginine are expressed as the incremental IRI and IRG areas under the respective curves for the 10-min period following the administration of arginine.[1,13] Basal values for insulin, glucagon, and glucose are taken as the mean of the four samples drawn over the 45-min control period before the first arginine pulse. Prestimulus insulin, glucagon, and glucose levels for the second and third arginine pulses are taken as the mean of the −15-, −10-, −5-, and 0-min values before administration of the arginine. The mean coefficients of variation for the pre-arginine stimulated glucose, insulin, and glucagon levels were 1.6%, 10.2%, 8.1%, respectively. The acute insulin and glucagon responses to arginine pulse I are designated AIR_I and AGR_I, respectively. A similar designation is used for the hormone responses to arginine pulses II and III. The modulating effect (Md) of glucose on the alpha-or beta-cells' response to arginine is calculated as the difference in IRG or IRI area between the two arginine pulses divided by the change in plasma glucose concentration. For example:

$$Md_{IRG} = \frac{AGR_I - AGR_{II}}{G_I - G_{II}}$$

Statistical analyses were performed by standard nonparametric and parametric tests.[24,25] Mean ± SEM values are shown and statistical significance is taken as $P < 0.05$ (two-tail).

RESULTS

Insulin. As shown in Table 1, mean glucose concentration in the nondiabetics was raised from glucose level I, 89 ± 3 mg/dl, to glucose level II, 159 ± 5 mg/dl, and to glucose

TABLE 1
Prestimulus glucose concentration (mg/dl) in the two subject groups at glucose levels I, II, and III

Subjects	Level I			Level II			Level III			M	
	Glucose	AIR	AGR	Glucose	AIR	AGR	Glucose	AIR	AGR	IRI	IRG
Nondiabetics (N = 16) I → II	89 ± 3	489 ± 74	852 ± 129	159 ± 5	1924 ± 300	424 ± 68				20 ± 3	−6.1 ± 1.0
Nondiabetics (N = 9) II → III				167 ± 7	2347 ± 481	551 ± 85	310 ± 22	5673 ± 1173	384 ± 71	23 ± 5	−1.2 ± 0.5
Non-insulin-dependent diabetics (N = 7) II → III				166 ± 14	689 ± 228	1128 ± 279	414 ± 29	1262 ± 286	905 ± 288	2.3 ± 0.5	−0.9 ± 0.4
Non-insulin-dependent diabetics (N = 5) II → I	99 ± 11	492 ± 168	1536 ± 169	195 ± 8	708 ± 239	935 ± 225				1.9 ± 0.6	−6.0 ± 1.2

The acute insulin response (AIR) and acute glucagon response (AGR) as mU/L/10 min and ng/L/10 min, respectively, are also given. Md_{IRI} and Md_{IRG} for the different subjects over the designated glucose changes are shown ($\bar{X}$ ± SEM).
Changes in plasma glucose levels I → II and II → III were brought about by glucose infusions and the change in glucose level II → I (in the diabetics) was brought about by an insulin infusion.

level III, 310 ± 22 mg/dl. These increases were accompanied by progressively greater mean AIR to arginine: AIR_I 489 ± 74, AIR_{II} 1924 ± 300, and AIR_{III} 5673 ± 1173 mU/L/10 min ($P < 0.01$, respectively, for all comparisons). A highly significant close correlation ($r = 0.87–0.95$) exists between the magnitude of the acute insulin response to arginine and the prestimulus glucose level ($r = 0.87$, glucose I–II; $r = 0.95$, glucose II–III)(Figure 2). Mean glucose concentration in the non-insulin-dependent diabetics at glucose level II was 166 ± 14 mg/dl and at glucose level III, 414 ± 29 mg/dl. These increases in glucose levels resulted in an increase of insulin responses from an AIR_{II} of 689 ± 228 to an AIR_{III} of 1262 ± 286 mU/L/10 min ($P < 0.01$). Lowering glucose level in the diabetics from glucose level II (195 ± 8 mg/dl) to level I (99 ± 11 mg/dl) resulted in a diminution of insulin response to arginine: AIR_{II} 708 ± 239 vs. AIR_I 492 ± 168 mU/L/10 min ($P < 0.01$).

The respective AIR vs. prestimulus glucose levels for the nondiabetics and NIDDM group are plotted in Figure 2. Individual AIR_I, AIR_{II}, and AIR_{III} for the non-insulin-dependent diabetics are shown. The slopes of these lines (Md_{IRI}) were determined from the subjects in the two groups and are summarized in Table 1. Md_{IRI} for nondiabetics over the glucose range level I to level II was the same as Md_{IRI} for the glucose range level II to level III. Although the diabetics did show a modulation effect, Md_{IRI} was markedly impaired in the non-insulin-dependent diabetics as compared with the nondiabetics, 1.9 ± 0.6 vs. 20 ± 3 ($P < 0.01$) for glucose level I to glucose level II, and 2.3 ± 0.5 vs. 23 ± 5 ($P < 0.01$) for glucose level II to glucose level III. As in nondiabetics, no difference in Md_{IRI} over the two glucose ranges was found for the type II diabetics. The Md_{IRI} for the obese, nondiabetic group was 37 ± 10.

A significant relationship was found to exist between the fasting plasma glucose of each subject and their Md_{IRI} value, although the slope of this relationship was different for the nondiabetics vs. the diabetics (see Figure 3). Individuals with greater IRI potentiation, the nondiabetics, have lower fasting glucose levels and diabetics who have greater impairment of modulation have higher fasting plasma glucose levels. The intersection of the nondiabetic and diabetic lines occurs at a plasma glucose level of approximately 110 mg/dl.

Figure 4 shows the linear relationship in the nondiabetics between the increase in AIR and the increase in prestimulus IRI caused by raising the plasma glucose level. In the non-insulin-dependent diabetics, although they had only small increments in AIR when made more hyperglycemic, this increase in AIR was appropriate for their prestimulus IRI rise since all points for the diabetics fall close to the nondiabetics' regression line.

Glucagon. The relationship between AGR and prestimulus plasma glucose level is shown in Table 1 and Figure 5. For the nondiabetic group, an increase in ambient glucose level from glucose level I to glucose level II resulted in a significant decrease in AGR (AGR_I 852 ± 129 vs. AGR_{II} 424 ± 68, ng/1/10 min $P < 0.01$). The increase in ambient glucose levels from glucose level II to glucose level III resulted in a significant further decrease in AGR, although the magnitude of this depression was significantly less than that seen for the first glucose increment. This difference in response over the two different glucose ranges is reflected in the different Md_{IRG} for the two glucose ranges: glucose level I to II, $Md_{IRG} = -6.1 \pm 1.0$ vs. glucose level II to III, $Md_{IRG} =$

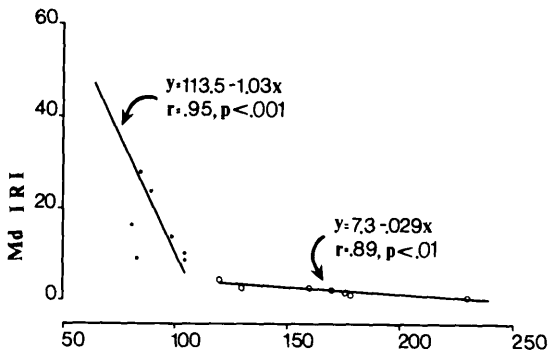


FIGURE 3. Relationship between nondiabetics (●) and diabetics' (○) fasting plasma glucose level and glucose potentiation of insulin responsiveness to arginine (Md_{IRI}).

FIGURE 2. Relationship between prestimulus plasma glucose concentration and the acute insulin response (AIR) mU/L/10 min to arginine in nondiabetics and non-insulin-dependent diabetics. The solid line (——) represents the linear regression in nondiabetics over glucose I→II and II→III. The range of values in nondiabetics are plotted as .——. Individual diabetics are plotted: o——o for glucose II→III and *—* for glucose II→I.

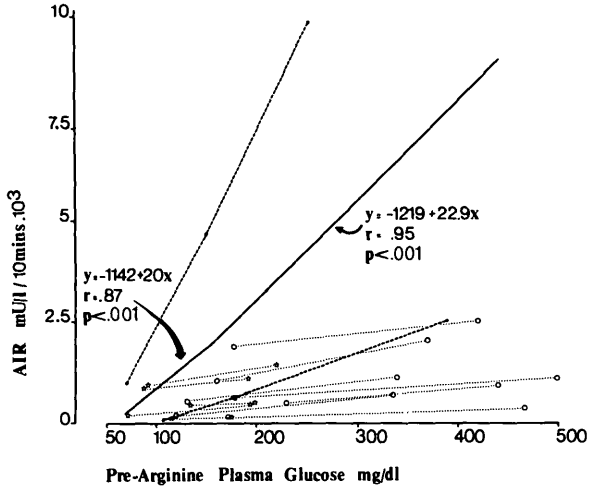
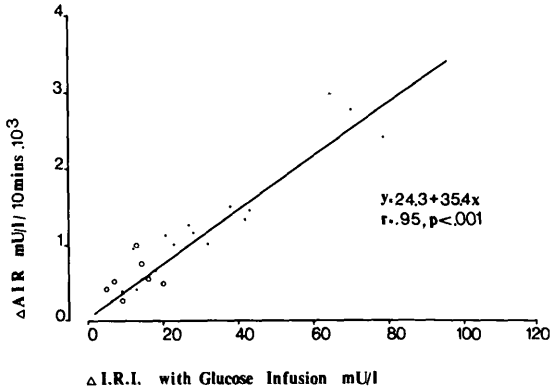


FIGURE 4. Relationship between the change in IRI (ΔIRI) and the change in acute insulin response to arginine (ΔAIR) (induced by the glucose infusion) in nondiabetics (●) and non-insulin-dependent diabetics (○). The regression line depicted is for the nondiabetics.



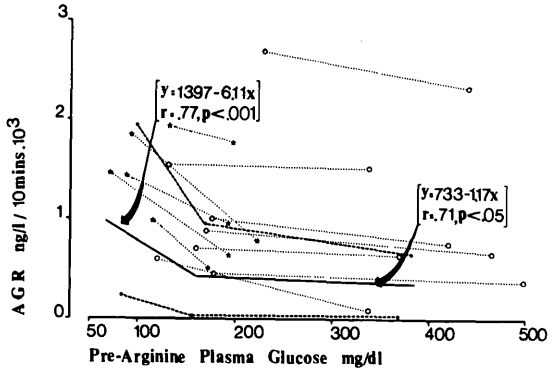


FIGURE 5. Relationship between prestimulus plasma glucose level and acute glucagon response (AGR) ng/L/10 min to arginine in nondiabetics and non-insulin-dependent diabetics. Designations otherwise as per Figure 2.

-1.2 ± 0.5 ($P < 0.01$). The relationship between AGR and prestimulus glucose level for each individual non-insulin-dependent diabetic and then the mean data for the groups are shown in Figure 5 and Table 1. An increase in the ambient glucose from level II to glucose level III in the diabetics resulted in a small but significant decrease in AGR with a mean Md_{IRG} of -0.9 ± 0.4, which was not significantly different from Md_{IRG} in the nondiabetics over this glucose range (-1.2 ± 0.5). Decreasing glucose concentration in the NIDDM group from level II to I resulted in an augmentation of the glucagon response to arginine. And, similar to nondiabetics, the Md_{IRG} over this glucose range was greater than Md_{IRG} over glucose range II to III. The Md_{IRG} of non-insulin-dependent diabetics over both glucose ranges did not differ significantly from the Md_{IRG} of the nondiabetics when compared over similar glucose ranges. No relationship was found between fasting glucose level and Md_{IRG} or AGR, or between Md_{IRG} and Md_{IRI} in either the nondiabetics or the diabetics.

DISCUSSION

In the present study, we investigated the ability of the ambient glucose level to modulate the acute responses of the pancreatic alpha- and beta-cells to arginine in nondiabetics and in non-insulin-dependent diabetics. Our results show that the modulating effect of glucose on the insulin response to arginine is clearly impaired in diabetics as compared with nondiabetics. In contrast, the modulating effect of glucose on the alpha-cell response to arginine appears to be normal in non-insulin-dependent diabetes when evaluated at glucose levels comparable to those in nondiabetics.

Many non-insulin-dependent diabetics are obese and insulin-resistant. Therefore, we performed studies in a group of normoglycemic but similarly obese subjects and found no impairment of the modulating effect of glucose on their acute hormonal responses to arginine. Thus, the results presented here for the non-insulin-dependent diabetics are not secondary to their obesity.

It is possible that the plasma glucose arterial-venous gradient is different in the diabetics and nondiabetics. However, it would be anticipated that this gradient would be lower in the diabetics. The diabetics have impaired insulin responses to glucose and thus the impairment of their Md_{IRI} compared with nondiabetics demonstrated by using plasma venous[16] rather than arterial samples is, if anything, underestimated. The possibility that insulin resistance in the diabetics would also result in a lower arterial-venous glucose gradient and thus again an underestimate of Md_{IRI} compared with nondiabetics is controlled for by the study in the obese group in whom a similar degree of insulin resistance would be anticipated.

In nondiabetics, the modulating effect of glucose on insulin responsiveness is constant over the range of plasma glucoses studied. Thus, the decreased modulating effect of glucose in non-insulin-dependent diabetics is not a result of their being on a different part of the glucose dose-response curve. As previously reported by Halter et al.,[16] the severity of the Md_{IRI} defect in non-insulin-dependent diabetics is related to their fasting plasma glucose. In nondiabetics, there was also a relationship between Md_{IRI} and fasting glucose concentration, but the slope of this relationship was much steeper than in the diabetics. The fact that the slope of potentiation is lower for the diabetic group than for nondiabetics indicates that a given change in plasma glucose provides less potentiation of insulin stimulation by arginine in this group than a similar change of glucose in nondiabetics. The highest Md_{IRI} was found in a diabetic with only a modest elevation of his fasting plasma glucose (120 mg/dl on the day of study), but this value was less than any Md_{IRI} in the normal subjects. Thus, nondiabetic normals can defend their basal plasma insulin levels by only a slight rise in plasma glucose concentration which potentiates non-glucose beta-cell stimulation, resulting in a rise in basal IRI level. In non-insulin-dependent diabetics, the much lower Md_{IRI} would result in greater levels of hyperglycemia being required to defend basal insulin secretion. And, with more severe defects in Md_{IRI}, it would be impossible, because of renal glucose loss, for hyperglycemia to fully compensate for the impaired Md_{IRI}. Such diabetics would then have marked fasting hyperglycemia, low basal IRI levels, and low AIR to nonglucose stimuli in the basal state. Halter and Porte have described such patients and have shown that this degree of fasting hyperglycemia is associated with the lowest AIR to isoproterenol.[16] The finding of a critical cutoff point between Md_{IRI} and fasting plasma glucose is similar to the relationship between the AIR to intravenous glucose and fasting plasma glucose reported by Brunzell et al.[26] Thus, our findings on the interaction of arginine and glucose support the concept that basal hyperglycemia in non-insulin-dependent diabetes may compensate for impaired glucose potentiation, thereby maintaining normal insulin secretory responses to nonglucose stimuli and consequently normal basal insulin levels.

Robertson and Porte have suggested that the decreased AIR to glucose in diabetics who have a normal response to a nonglucose secretogogue like isoproterenol might be explained by the existence of different receptors for the two stimuli on the beta-cell.[9] The fact that the beta-cell in diabetes can respond normally to a nonglucose stimulus suggests that the defect in the beta-cells' response to glucose is one of recognition rather than a secretory defect per se. A defective receptor for glucose recognition in diabetics could explain not only the defect in stimulation by glucose but the concept can be extended to explain the impaired modulating effect of glucose in diabetes as well. Figure 4, which shows the close relationship between the change in AIR to arginine and the change in prestimulus IRI level

brought about by the glucose infusion in the nondiabetics, suggests that both in normals and non-insulin-dependent diabetics the potentiation of AIR by hyperglycemia is directly proportional to the degree of direct stimulation that glucose applies to the pancreatic beta-cell. The rise in IRI brought about by the glucose infusion is much less in the non-insulin-dependent diabetics, but their increase in AIR is appropriate for the IRI rise. Several of the nondiabetics had IRI increments similar to the diabetics (but in response to a much smaller rise in plasma glucose) with similar changes in AIR response. If a decreased number of beta-cells or decreased secretory capacity were the islet in non-insulin-dependent diabetes, one might expect that the ability to respond to a maximal stimulus like 5 g of arginine[1,13] would be more impaired than the response to mild elevations in glucose, and therefore the diabetic points would lie below the normal line (Figure 4). Since the values in the diabetics are clustered around the normal line, this provides further evidence that the impaired Md_{IRI} seen in NIDDM is not secondary to a beta-cell secretory deficiency but rather a failure to recognize the glucose stimulus.

In contrast with the impaired Md_{IRI} seen in the non-insulin-dependent diabetics, this study demonstrated that over similar changes in prestimulus glucose levels, the Md_{IRG} for normals and the NIDDM group is not significantly different. The acute glucagon responses to arginine (which is predominantly 3500-dalton glucagon of pancreatic origin) in nondiabetics showed a sharp decrement over the glucose range 89–159 mg/dl. However, greater degrees of hyperglycemia were much less potent in inhibiting the glucagon response. A similar biphasic pattern for Md_{IRG} was observed in the diabetics over the two glucose ranges. It appears that the fasting hyperglycemia seen in the NIDDM group has placed them on the relatively flat part of the normal glucagon response curve. The markedly different Md_{IRG} over glucose ranges I and II compared with Md_{IRG} over glucose ranges II and III is in marked contrast to the modulation of insulin secretion, which is constant over the complete range of glucose evaluated in either the nondiabetics or the diabetics. The level of plasma glucose at which the slope of the glucagon response curve (Md_{IRG}) changes abruptly is approximately 160 mg/dl. This value may actually be closer to the normal fasting blood glucose level since our experimental protocol did not evaluate glucose concentrations between fasting and 160 mg/dl.

Previous investigations of insulin and glucagon secretion in non-insulin-dependent diabetics have usually compared secretory responses in nondiabetics and diabetics in the basal state, that is, after an overnight fast.[9,11–13] By definition, the two populations are consequently studied at different glucose concentrations, and it has been argued that comparisons should be made with the nondiabetics made hyperglycemic or after normoglycemia has been induced in the diabetics. But this results in only one of the populations being in the basal state. Our current observation that glucose potentiation of insulin responsiveness is impaired in non-insulin-dependent diabetics in direct proportion to their relative fasting hyperglycemia suggests that the "effective" glucose level that the beta-cell responds to is decreased in non-insulin-dependent diabetics. At their fasting glucose levels, this "effective" glucose level is equivalent in normoglycemic nondiabetics and hyperglycemic non-insulin-dependent diabetics. Therefore, if we are correct in our hypothesis that the defect in glucose modulation of insulin responsiveness to nonglucose stimuli plays a major role in determining the degree of hyperglycemia, then to quantify beta-cell responsiveness to nonglucose stimuli, both non-insulin-dependent diabetics and nondiabetics should be studied at their respective fasting glucose levels. But, since insulin resistance may play a role in determining the degree of fasting hyperglycemia, the "correct" level of plasma glucose at which studies in NIDDM should be performed is probably a little below basal (their fasting). In contrast, the normal modulating effect of glucose on alpha-cell responsiveness would imply that for glucagon secretion, diabetics and nondiabetics should be studied at similar glucose concentrations.

This study has shown that potentiation of beta-cell responsiveness by increments in glucose concentration is markedly impaired in non-insulin-dependent diabetics compared with nondiabetics. The degree of this impairment in the diabetics is inversely related to their basal glucose level. Thus, in non-insulin-dependent diabetics, basal hyperglycemia could compensate for the impaired glucose modulation of beta-cell responsiveness to nonglucose secretogogues, thereby maintaining normal basal plasma insulin levels. From the limited data in this study, it appears that this impaired glucose modulation is a result of failure to recognize the glucose stimulus rather than a beta-cell secretory defect per se. In contrast, the negative modulating effect of hyperglycemia on the glucagon response to arginine is inversely related to the ambient plasma glucose concentration and is biphasic. And the modulating influence of glucose concentration on alpha-cell responsiveness is normal in NIDDM when differences in glucose level are taken into account. This modulating action of glucose on glucagon secretion may be part of the mechanism that maintains the compensatory basal hyperglycemia of non-insulin-dependent diabetics.

ACKNOWLEDGMENTS

The authors are grateful fo Rose Potts and Julie Holly for their excellent technical assistance, and to Sylvia MacMillan and Jean Williamson for typing the manuscript.

This work was supported, in part, by NIH grant AM17047, USPHS grant SEA 790878, and a grant from the Juvenile Diabetes Foundation. Dr. Asplin is the recipient of a Fellowship Award from the American Diabetes Association, Washington Affiliate, and an award from the Oxford Regional Health Authority. Dr. Hollander was the recipient of a National Institutes of Health Research Fellowship (AM06118). Dr. Palmer is the recipient of a Clinical Investigator Award (1K08 AM 00535).

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