Interaction of Glucose and Epinephrine in the Regulation of Insulin Secretion

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SUMMARY

To determine whether the elevated plasma glucose levels produced by epinephrine (EPI) in vivo offset important islet effects of EPI in man, the acute insulin responses (AIR: $\bar{x}$ IRI Δ 2–5 min) to 5 g i.v. arginine were measured at varying EPI and glucose levels. After infusion of EPI at 80 ng/kg/min for 45 min, achieving venous plasma EPI levels of 1140 ± 121 pg/ml, the AIR was indistinguishable from that seen in 10 untreated subjects (EPI versus untreated: 59 ± 11 versus 41 ± 5 μU/ml, $\bar{x}$ ± SEM, P = NS), but plasma glucose had risen to 165 ± 8 mg/dl. When this glucose rise was matched in each subject by a glucose clamp infusion (GLU) with no EPI infusion, AIR increased to 467 ± 82% of that during EPI (N = 8, P < 0.001). With glucose subsequently clamped at a higher level, 256 ± 5 mg/dl, the AIR to arginine during GLU alone was 220 ± 17% of that during EPI + GLU (N = 7, P < 0.001). A qualitatively similar inhibitory effect on AIR to arginine was also observed using a lower dose of EPI (15 ng/kg/min, giving a venous plasma EPI level of 192 ± 19 pg/ml). To quantitate the opposing effects of plasma glucose and EPI on the AIR to arginine, a multiple linear regression analysis using glucose and EPI levels was performed. This analysis showed that AIR is positively correlated with plasma glucose ($P \ll 0.001$), negatively correlated with log [EPI] ($P \ll 0.001$), and negatively correlated with their product, glucose × log [EPI] (P < 0.01). The changes in glucose and EPI explained 90% of the variation in AIR observed within each subject ($R^2 = 0.896$). These studies demonstrate that EPI inhibits AIR to arginine over a wide range of glucose levels, but that the B-cell-stimulating effect of hyperglycemia can obscure this inhibition. The data suggest that the development of hyperglycemia during stress states may compensate for the inhibitory effect of EPI on B-cell function, thereby maintaining normal basal and stimulated insulin levels. DIABETES 31:802–807, September 1982.

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Acute administration of epinephrine (EPI) inhibits both basal- and glucose-stimulated insulin release by an α-adrenergic mechanism.[1] This immediate inhibitory effect on B-cell function contributes to the hyperglycemia observed during stress states such as acute myocardial infarction, burn injury, and surgery.[2] However, during more prolonged administration of EPI and during persistent stress states, circulating insulin levels return to normal, or may even be elevated,[3,4] despite continued unresponsiveness to a glucose challenge.[5] Furthermore, insulin secretory responses to non-glucose stimuli appear to be unaffected.[6–8]

In addition to directly stimulating insulin release, glucose also modulates B-cell function by augmenting responsiveness to a variety of non-glucose secretagogues.[9–11] Therefore, it is possible that during epinephrine infusion or during stress states, hyperglycemia may offset α-adrenergic depression of B-cell responses by potentiating responses to nonglucose secretagogues. The result might be maintenance of relatively normal basal insulin levels and insulin responses to nonglucose stimuli during stress states, but at an elevated circulating glucose level. The present studies were designed to evaluate the role of hyperglycemia to modulate adrenergic inhibition of insulin secretion by quantitating the interaction of circulating EPI and glucose levels in the regulation of B-cell function. To achieve this, we measured insulin responses to arginine during EPI infusions in man, while controlling glucose levels.

MATERIALS AND METHODS

STUDY SUBJECTS

Eight normal male volunteers underwent study on three separate days. An additional 10 men were studied on only one occasion. All were outpatients and were on an ad libitum diet. None had any known illnesses or had been using med-

ications within the 2 wk before the study. Aspirin and aspirin-containing products were specifically excluded for at least 1 wk before the study.[12] Subjects ranged in age from 23 to 53 yr (median 31) and their body weights ranged from 95% to 145% (median 108%) of ideal (Metropolitan Life Insurance Company Tables, 1959). Each subject's fasting plasma glucose level was less than 110 mg/dl, and no subject had a history of diabetes in first- or second-degree relatives.

STUDY CONDITIONS

Informed consent was obtained from all subjects before study. All studies were begun at 8:00 a.m. after an overnight fast; subjects specifically abstained from cigarettes, coffee, and tea after midnight. Each study was performed with the subjects supine; scalp vein needles were placed in antecubital veins of each forearm and kept patent with a slow infusion of 0.9% NaCl. One line was used for blood sampling and the other for administration of drugs.

PROTOCOLS

Eight subjects were each studied on three separate days: On the first day they received high-dose epinephrine (High EPI), on the second day, low-dose epinephrine (Low EPI), and on the third day, no EPI infusion (glucose alone). Study days for each subject were separated by a week or more. Samples drawn at 15, 25, and 30 min after needle insertion were used for estimation of basal plasma glucose and insulin and those at 25 and 30 min for estimation of plasma catecholamines.

High-dose EPI (day 1). Following the 30-min baseline period, an i.v. infusion of EPI (Parke-Davis) at a rate of 80 ng/kg/min was begun. Samples for measurement of plasma glucose and insulin were obtained after 15, 30, 40, and 45 min of EPI infusion, and samples for plasma catecholamine measurement after 40 and 45 min of infusion. At 45 min, 5 g of arginine HCl, as the 10% solution, was injected i.v. in 25 s or less. This dose has been shown to be maximal for insulin release in man.[13] Blood samples for plasma insulin and plasma glucose measurement were obtained at 2, 3, 4, 5, 6, 10, and 30 min after arginine injection. Then, a 45-min variable-rate glucose infusion was started to bring the glucose level to approximately 250 mg/dl and maintain it there, using a technique described in detail below. Samples for insulin and glucose levels were obtained at 15, 30, 40, and 45 min and for catecholamines at 40 and 45 min after the start of this glucose clamp period. At 45 min, another injection of 5 g of arginine was given and samples were obtained as before for measurement of plasma insulin and glucose. A previous study[13] has shown that prior arginine injections do not affect the acute incremental insulin response to arginine.

Low-dose EPI (day 2). After the 30-min baseline period, an EPI infusion of 15 ng/kg/min was begun and continued throughout. Forty-five minutes into this infusion, an i.v. arginine pulse was given. Next, glucose was infused at a variable rate to bring the glucose level to that observed after 45 min of High-EPI infusion (on day 1), and a second arginine pulse was given. Thirty minutes after the second arginine pulse, in 5 of the 8 subjects, a variable-rate glucose infusion was used to bring the glucose level to approximately 250 mg/dl, and a third arginine pulse was given. Blood samples for measurement of insulin, glucose, and catecholamines were obtained before and after each arginine pulse, as on day 1.

Glucose alone (day 3). Following the baseline period, a variable glucose infusion was given for 45 min to duplicate the mild hyperglycemia previously produced in that subject by 45 min of Low-EPI infusion, and an arginine pulse was given. Subsequently, glucose was clamped to the level produced by 45 min of High EPI, and a second arginine pulse was given. Finally, in 7 of the 8 subjects, the glucose level was raised to approximately 250 mg/dl, and a third arginine pulse was given.

No infusions. An additional 10 men were studied once at basal glucose levels. After i.v. placement and baseline sampling, as described above, 5 g of arginine was injected and samples were obtained at 2, 3, 4, 5, 6, 10, and 30 min for measurement of glucose and insulin.

Variable-rate glucose infusion. Plasma glucose was raised to desired levels and stabilized there by means of variable-rate infusions of 10% dextrose. Glucose levels were monitored at the bedside, using a Beckman Glucose Analyzer (Beckman Instruments Inc., Fullerton, California) to assay samples obtained every 5 min during each 45-min variable-infusion period. These readings provided input to a programmable calculator that determined glucose infusion rates. The calculator implemented a negative feedback algorithm based on that devised to control the Biostator (Miles Laboratories, Elkhart, Indiana) closed-loop artificial pancreas system:[14]

$$\text{Glucose infusion rate (mg/min)} = MR\left(1 + \frac{GD - G_0}{120\ \text{mg/dl}}\right)^4$$

$$\text{for } \frac{GD - G_0}{120} + 1 > 0$$

$$\left[\text{Glucose infusion rate} = 0 \text{ for } \frac{GD - G_0}{120} + 1 \leq 0\right]$$

where MR (maintenance rate) is a glucose infusion rate (in mg/min) estimated to be sufficient to maintain plasma glucose at the desired level (GD), G_0 is the current measure of plasma glucose, and 120 mg/dl is an empirically selected damping factor. A previously calibrated peristaltic pump delivered the glucose solution at the desired rates.

ANALYTIC METHODS

For measurements of plasma insulin and glucose levels, 5-ml blood samples were collected in EDTA and stored on ice until the end of the day's procedure. The plasma was then separated at 4°C and frozen at −20°C for subsequent analysis. Plasma immunoreactive insulin (IRI) levels were measured with a modification of the double-antibody technique of Morgan and Lazarow.[15] To ensure comparability, all samples from a given subject were assayed for insulin in a single assay. Plasma glucose was measured with the AutoAnalyzer glucose-oxidase method (Technicon Instruments, Tarrytown, New York). (Glucose levels determined at the bedside were used only to adjust the rate of glucose infusion.) Basal glucose and insulin levels were calculated as the mean of the three values obtained during the baseline period. Prestimulus levels are expressed as the mean of the two samples taken 5 min before and immediately before the injection of arginine. The acute insulin response (AIR) to arginine was calculated as the mean elevation above pre-

stimulus level of the insulin values at 2, 3, 4, and 5 min after arginine injection.

For measurement of plasma epinephrine and norepinephrine, 2.5 ml of blood was collected in prechilled glass tubes containing EGTA and glutathione and placed on ice immediately. Within 45 min, the plasma was centrifuged twice at 4°C and then frozen at −20°C for subsequent analysis by the single isotope enzymatic assay as previously described.[16]

STATISTICAL ANALYSIS

For comparisons among more than two conditions, a two-way (subjects by treatments) nonparametric analysis of variance using Friedman rank sums was employed; the hypothesis that a monotonic rising (or falling) order is present was tested against the null hypothesis (that the proposed order is not present) by the method of Page.[17] When only two groups were compared, the Wilcoxon signed ranks test was used.[18] To quantitate the influence on AIR of variables such as plasma glucose level and EPI level, a stepwise multiple linear regression analysis was performed using the SPSS program[19] on a HP 3000 computer. As each parameter was introduced, an analysis was made of the improvement in fit of the model to the observed data. Those parameters that produced a statistically significant improvement in fit were retained in the final model.

Since individuals may vary in their sensitivity to each modulating variable (expressed by the coefficient of that variable), the procedure used allowed for differences between individuals in each coefficient, wherever such individualization across subjects produced an improvement in fit that was statistically significant. For example, if a statistically significant improvement in fit were obtainable by individualizing the coefficient that expresses the effect of glucose level (on AIR), the model would individualize it so that eight coefficients (one per subject) would be estimated; otherwise one coefficient for this effect would be assigned to the whole group. Constraining all subjects to have the same "intercept" term would introduce distortion into the estimation of the coefficients; therefore individualized intercept terms were estimated, irrespective of any resulting improvement in fit.

RESULTS

Effect of hyperglycemia on insulin levels and responses. Infusion of 15 ng/kg/min of EPI (Low EPI) produced a plasma EPI level of 192 ± 19 pg/dl (mean ± SEM), comparable to levels seen during moderate physiologic stress.[20] During Low EPI, as shown in Figure 1, raising the glucose level from 101 ± 2 to 172 ± 9 to 250 ± 9 mg/dl raised prestimulus insulin from 12 ± 1 to 26 ± 3 to 65 ± 9 μU/ml ($P < 0.001$, by Page's test) and produced a fivefold increase in the incremental AIR to a 5-g bolus injection of arginine (from 49 ± 6 to 138 ± 17 to 319 ± 34 μU/ml, $P < 0.001$).

Infusion of 80 ng/kg/min of EPI (High EPI) produced a plasma EPI level of 1140 ± 121 pg/ml, comparable to levels seen during severe physiologic stress.[20] Despite this, as shown in Figure 2, raising the glucose level from 165 ± 8 to 266 ± 7 mg/dl raised prestimulus insulin from 11 ± 2 to 27 ± 4 μU/ml ($P < 0.02$, Wilcoxon) and nearly tripled the incremental AIR to arginine, from 59 ± 11 to 170 ± 26 μU/ml ($P < 0.02$, Wilcoxon).

In the presence of glucose infusions alone (control), plasma EPI stayed at basal levels of 47 ± 7 pg/ml. The stepwise increases in glucose level again produced stepwise increases in insulin levels and AIR (both $P < 0.001$, Page). The AIRs to arginine during glucose infusion alone are summarized in Figure 3 and are compared with those observed during Low EPI and High EPI. During all three treatments, the AIR to arginine increased as the plasma glucose level was raised.

Effect of EPI on insulin responses at matched glucose levels. Since responses to arginine were obtained at the same glucose levels during each treatment, it is possible to examine the effect of differences in EPI level with glucose held constant (Figure 4). At a glucose level averaging 102 ± 2 mg/dl, the AIR to arginine was lower in every subject during Low EPI than during glucose alone ($P < 0.008$, Wilcoxon; means 77 ± 13 versus 49 ± 6 μU/ml). At a glucose of 166 ± 5 mg/dl, increasing the EPI caused a stepwise reduction in every subject ($P < 0.001$, Page; means 232 ± 35 versus 138 ± 17 versus 59 ± 11 μU/ml). Stepwise inhibition of AIR by increasing EPI level was also seen at PG = 256 ± 5 mg/dl ($P < 0.001$, Page).

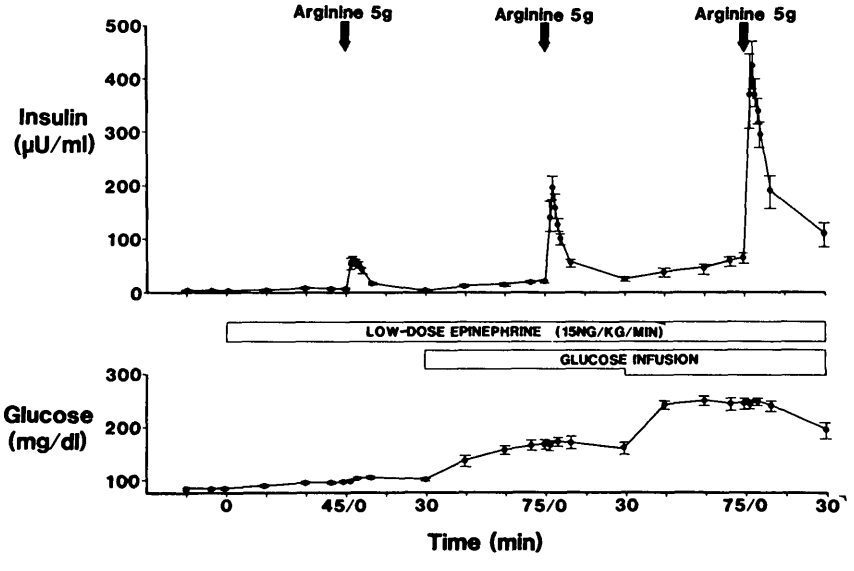


FIGURE 1. Acute insulin responses to 5 g of arginine during Low-EPI infusion, then after stepwise further hyperglycemia was produced by variable-rate glucose infusion (N = 8).

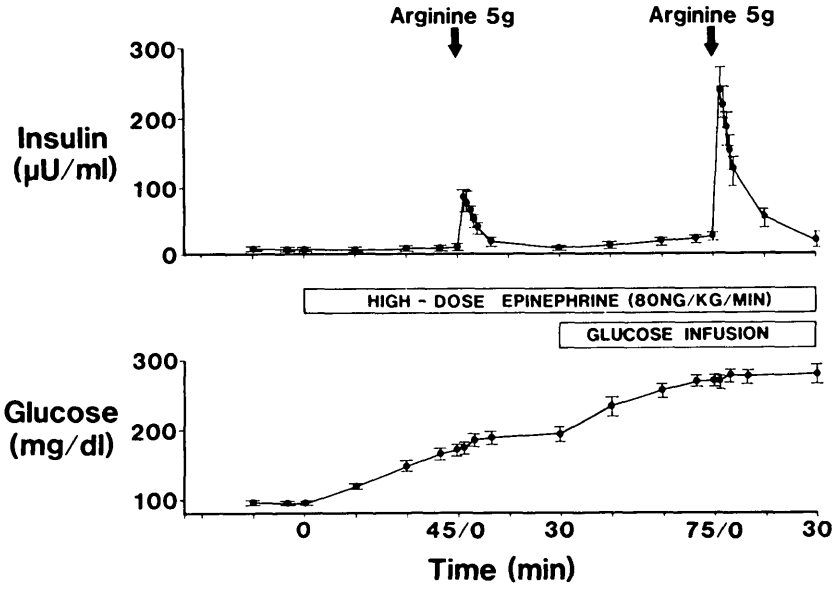


FIGURE 2. Acute insulin responses to 5 g of arginine during High-EPI infusion, then after further hyperglycemia was produced by variable-rate glucose infusion (N = 8).

When assessed without taking into account the plasma glucose level, the effects of EPI on AIR to arginine may appear minimal. For example, when the response (59 ± 11 μU/ml) at the spontaneous level of hyperglycemia during High EPI is compared with a control response (77 ± 13 μU/ml), obtained at minimal hyperglycemia, little inhibitory effect of EPI is apparent ($P > 0.10$, Wilcoxon). A separate group of 10 normal men given no glucose infusion (prestimulus PG = 93 ± 3 mg/dl) had an AIR to 5 g of arginine (41 ± 5 μU/ml) that tended to be less than the AIR observed here during High EPI (though not statistically distinguishable by nonpaired comparison).

Regression analysis. The AIR to arginine was a linear function of prestimulus glucose level during glucose alone ($r = 0.89$), during Low EPI ($r = 0.90$), and during High EPI ($r = 0.86$). To determine whether high circulating EPI levels reduce islet sensitivity to changes in glucose level, the relationship of AIR to glucose level during High EPI was compared with that during glucose alone, as illustrated in Figure 5. The regression slope ΔAIR/Δglucose was measured for each treatment in each subject. In every subject, this slope was greater during glucose alone than during High EPI ($P < 0.02$, Wilcoxon). The median slope declined from 2.37 during glucose alone to 1.87 during Low EPI to 0.70 during High EPI.

A multiple linear regression model was used to analyze the influence of the prestimulus glucose and EPI levels on the AIR to arginine. The model was fitted to the data in steps; potentially predictive variables such as EPI level were added to the model one by one and were retained only if their inclusion caused a statistically significant improvement in fit. (Table 1 gives details of the model and the results of significance tests for inclusion of parameters.) The analysis showed that glucose and EPI levels, and their product, are significant predictors of AIR to arginine. The coefficients for glucose × log [EPI] differed significantly among subjects and are individualized in the final model. The coefficients for glucose and for log [EPI] did not differ appreciably among subjects, so the same coefficients were used for all subjects. The relationships between prestimulus glucose and EPI levels and the AIR to arginine, as fitted to one of the study subjects by the model, are illustrated in Figure 6. The surface demonstrates how AIR rose with increasing glucose level and fell with increasing EPI level. The curva-

FIGURE 3. Acute insulin responses to 5 g of arginine, grouped by prestimulus EPI level, showing the effect of stepwise increases in glucose level. There is a stepwise increase in AIR within each group, $P < 0.008$ to $P < 0.001$, N = 8.

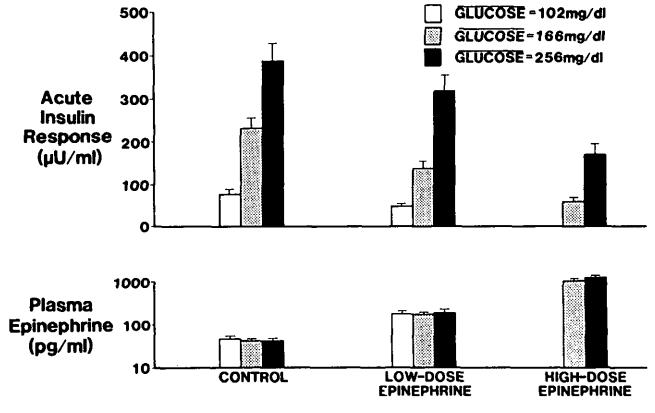
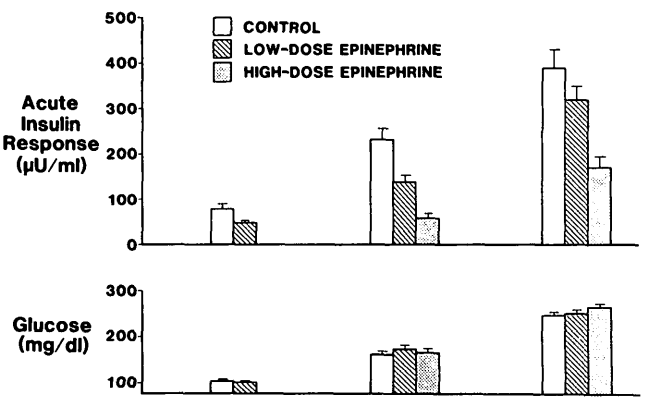


FIGURE 4. Acute insulin responses (AIR) to 5 g of arginine, grouped by prestimulus glucose level, showing the effect of increases in EPI level. At each glucose level, increasing the EPI level caused a stepwise decrease in AIR ($P < 0.008$ to $P < 0.001$, N = 8).



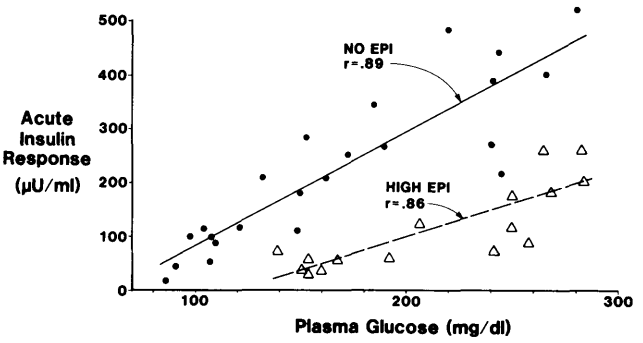


FIGURE 5. Relationship of acute insulin response to prestimulus glucose during control study using glucose alone (solid line) and during High EPI (broken line). Each subject's slope during High EPI was lower than during glucose alone ($P < 0.02$).

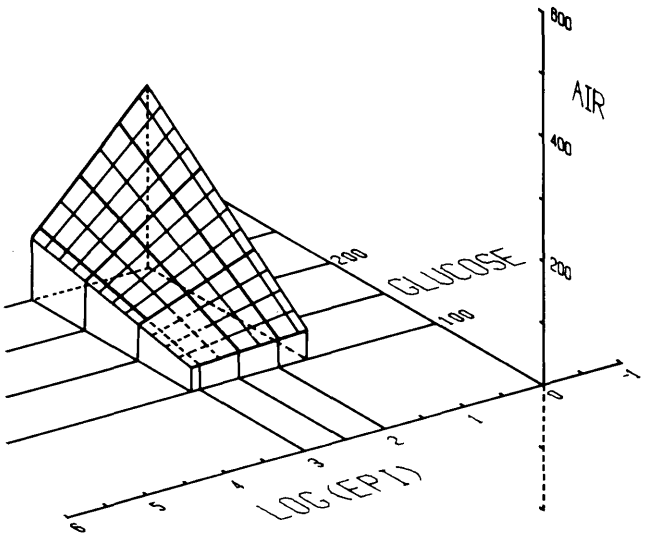


FIGURE 6. Relationship of acute insulin response (AIR) to prestimulus glucose (G) and EPI levels. The regression surface produced by the model for one subject in the study group is shown. (AIR = 3.2 G − 2.9 log [EPI] − 0.74 × G × log [EPI] − 123.) The twisting of the surface comes from the interaction term (the coefficient of G × log [EPI]), which decreases the influence of glucose at high EPI levels. (Solid lines on surface indicate domains actually tested; broken lines indicate extrapolation.)

ture of the surface is due to a significant interaction of these two variables, whereby the effect of a change in glucose level was greater when the EPI level was basal than when it was high. The overall coefficient of determination (R^2) for the model was 0.90, indicating that the regression, using prestimulus glucose and EPI levels, explained 90% of the observed variation in AIR within each subject.

DISCUSSION

The present study was designed to quantitate glycemic modulation of B-cell response to non-glucose stimulation during physiologic elevations of EPI. The results show that changes in glucose level modulate the secretory response to arginine during mild or marked physiologic elevations of EPI very much as they do at basal EPI levels: The AIR to arginine is a linear function of glucose level under each of the three conditions. However, the regression slope relating AIR to glucose level is reduced during marked EPI elevation compared with the control study (Figure 5), indicating that EPI reduces the "gain" of hyperglycemic amplification of response. Nonetheless, the AIR remains closely governed by glucose level during EPI elevations, and an increase of glucose level from 166 to 256 mg/dl causes an increase in mean response of 188% during the High-EPI infusion (Figure 3; right).

Previous studies in man have shown at least as great an insulin secretory response to non-glucose secretagogues during EPI infusion as during saline control, whether the stimulus was arginine, alanine, or secretin.[6–8] In contrast, studies in vitro or in perfused pancreas preparations have shown EPI to attenuate such responses.[21,22] The present studies strongly suggest that this apparent discrepancy is due to the hyperglycemia that results from EPI in vivo and opposes the direct B-cell inhibitory effect of EPI. For example, with glucose levels matched at 166 ± 5 mg/dl, the acute insulin response (AIR) to a 5-g injection of arginine is clearly depressed below control by High-EPI infusion (Figure 4). When this AIR during High EPI is compared with a control response obtained at a lower prestimulus glucose level (102 ± 3 mg/dl), the inhibitory effect of epinephrine is barely discernible. The response to an arginine pulse given at a basal glucose level actually tended to be less than the AIR during a High-EPI infusion. Thus, the inhibitory effect of

TABLE 1
Significance of parameters influencing the acute insulin response (AIR) to arginine

Parameter added	Form of model	Improvement in fit from including parameter		R^2 with parameter included
		F	P	
Individual mean AIR	$AIR = a_i$	—	—	0.152
Glucose (G) level (coefficient not individualized)	$AIR = a_i + bG$	$F_{(1,51)} = 40.6$	$\ll 0.001$	0.528
Log [EPI level] (coefficient not individualized)	$AIR = a_i + bG + c \log [EPI]$	$F_{(1,50)} = 83.7$	$\ll 0.001$	0.823
G × log [EPI] (not individualized)	$AIR = a_i + bG + c \log [EPI] + dG \log [EPI]$	$F_{(1,49)} = 7.66$	<0.01	0.847
G × log [EPI] (using subject-specific coefficient)	$AIR = a_i + bG + c \log [EPI] + d_iG \log [EPI]$	$F_{(7,42)} = 2.83$	<0.025	0.896

epinephrine on responses to non-glucose secretagogues, which amounts to a 37–74% decrement in the present studies, is effectively masked by epinephrine-induced hyperglycemia. Although the present study does not exclude some duration-dependent component to the effect of hyperglycemia on insulin responses, the duration of hyperglycemia was matched as closely as possible between epinephrine-treated and control protocols. As a result, the differences in AIR between treatments are attributable to the differences in EPI level.

The finding that EPI is a dose-dependent inhibitor of insulin-secretory response to arginine when glucose levels are matched accords with the results of Efendic et al.,[23] who used arginine infusion (rather than injection) as a stimulus. The present study goes on to quantitate the effect of epinephrine on the sensitivity of the B-cells to potentiation by hyperglycemia. This sensitivity to glucose level is expressed by the slope relating AIR to prestimulus glucose level, a slope that was lower in each subject during High EPI than during the control study. In the multiple regression analysis, this decline in sensitivity to glucose level is expressed by the fact that the coefficient of the product of glucose and log [EPI] is negative. This interaction twists the regression surface (Figure 6), making a change in glucose level have less effect at a high EPI level than at a low one.

The precision with which islet responsiveness to arginine is regulated by EPI and glucose levels is evident from the multiple regression analysis. The "best fit" regression model predicts AIR, based on prestimulus EPI and glucose levels; using the variations in these levels, the model can account for 90% of the observed AIR variation within a subject. Thus, when other factors are not manipulated, EPI and glucose levels together provide a powerful description of the readiness of the endocrine pancreas to secrete insulin in response to an amino acid stimulus.

Adrenergic suppression of the response to non-glucose secretagogues, demonstrated here for arginine, suggests a mechanism whereby the effects of stress on the islet both promote and regulate hyperglycemia. Basal insulin secretion may be thought of as an integrated response to ambient non-glucose stimulants, as modulated by plasma glucose level.[24] When EPI levels rise as part of the stress response, basal insulin secretion is suppressed.[3] This suppression, along with the direct hepatic and peripheral effects of the stress hormones,[25,26] causes the glucose level to rise. EPI inhibits the islet's direct response to this glucose rise, just as it inhibits the response to an i.v. glucose pulse,[5] but it does not prevent the hyperglycemia from amplifying the response to nonglucose stimulation. Thus, insulin levels rise as glucose levels rise. The β-adrenergic effect of EPI provides increased non-glucose stimulation to the islet, presumably also contributing to the resurgence of insulin. Eventually, a new steady state is reached in which circulating insulin has risen enough to bring peripheral glucose uptake and hepatic glucose output into balance with each other, preventing any further glucose rise. Because of the stress-hormone-induced hepatic and peripheral insulin resistance, this balance point often requires a higher insulin level than is needed to maintain glucose homeostasis in the unstressed state. Thus, insulin levels may be high during stress,[4] even though EPI is inhibiting B-cell function to allow hyperglycemia.

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REFERENCES

1. Porte, D., Jr.: A receptor mechanism for the inhibition of insulin release by epinephrine in man. J. Clin. Invest. *46*:86–94, 1967.
2. Woods, S. C., Smith, P. H., and Porte, D., Jr.: The role of the nervous system in metabolic regulation and its effects on diabetes and obesity. *In* Handbook of Diabetes Mellitus: Intermediary Metabolism and Its Regulation. Vol. 3. Brownlee, M., Ed. New York, Garland STPM Press, 1981, pp. 209–72.
3. Robertson, R. P., and Porte, D., Jr.: Adrenergic modulation of basal insulin secretion in man. Diabetes *22*:1–8, 1973.
4. Vitek, V., Land, D. J., and Cowley, R. A.: Admission serum insulin and glucose levels in 247 accident victims. Clin. Chim. Acta *95*:93–104, 1979.
5. Lerner, R. L., and Porte, D., Jr.: Epinephrine: selective inhibition of the acute insulin response to glucose. J. Clin. Invest. *50*:2453–57, 1971.
6. French, J. W., Porte, D., Jr., and Baum, D.: The effect of hypoxia and epinephrine infusion on arginine-induced insulin release. Proc. Soc. Exp. Biol. Med. *144*:288–90, 1973.
7. Conway, M., Freidrich, J., Schade, D., Buckman, M., and Eaton, R. P.: The effect of altered autonomic tone on alanine induced insulin secretion. Horm. Metab. Res. *10*:290–94, 1978.
8. Lerner, R. L., and Porte, D., Jr.: Studies of secretin-stimulated insulin responses in man. J. Clin. Invest. *51*:2205–10, 1972.
9. Floyd, J. C., Fajans, S. S., Pek, S., Thiffault, C. A., Knopf, R. F., and Conn, J. W.: Synergistic effect of certain amino acids and glucose upon insulin secretion in man. Diabetes *16*:510–11, 1967.
10. Halter, J. B., Graf, R. J., and Porte, D., Jr.: Potentiation of insulin secretory responses by plasma glucose levels in man: evidence that hyperglycemia in diabetes compensates for impaired glucose potentiation. J. Clin. Endocrinol. Metab. *48*:946–54, 1979.
11. Taborsky, G. J., Smith, P. H., Halter, J. B., and Porte, D., Jr.: Glucose infusion potentiates the acute insulin response to nonglucose stimuli during the infusion of somatostatin. Endocrinology *105*:1215–20, 1979.
12. Robertson, R. P.: Prostaglandins as modulators of pancreatic islet function. Diabetes *28*:943–48, 1979.
13. Palmer, J. P., Walter, R. M., and Ensinck, J. W.: Arginine-stimulated acute phase of insulin and glucagon secretion. 1. In normal man. Diabetes *24*:735–40, 1975.
14. Clemens, A. H.: Feedback control dynamics for glucose-controlled insulin infusion systems. Med. Prog. Technol. 6:91–98, 1979.
15. Morgan, C. R., and Lazarow, A.: Immunoassay of insulin: two-antibody system. Diabetes *12*:115–26, 1963.
16. Evans, M. L., Halter, J. B., and Porte, D., Jr.: Comparison of double- and single-isotope enzymatic derivative methods for measuring catecholamines in human plasma. Clin. Chem. *24*:567–70, 1978.
17. Hollander, M., and Wolfe, D. A.: Nonparametric Statistical Methods. New York, John Wiley and Sons, 1973, pp. 27–33.
18. Hollander, M., and Wolfe, D. A.: Nonparametric Statistical Methods. New York, John Wiley and Sons, 1973, pp. 147–50.
19. Nie, N. H., Hull, C. H., Jenkins, J. G., Steinbrenner, K., and Bent, D. H.: Statistical Package for the Social Sciences. New York, McGraw-Hill, 1975, pp. 320–67.
20. Cryer, P. E.: Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. N. Engl. J. Med. *303*:436–44, 1980.
21. Rabinovitch, A., Cerasi, E., and Sharp, C. W. G.: Adenosine 3',5'-monophosphate-dependent and -independent inhibitory effects of epinephrine on insulin release in rat pancreatic islets. Endocrinology *102*:1733–40, 1978.
22. Burr, I. M., Slonim, A. E., and Sharp, R.: Interactions of acetylcholine and epinephrine on the dynamics of insulin release in vitro. J. Clin. Invest. *58*:230–39, 1976.
23. Efendic, S., Luft, R., and Cerasi, E.: Quantitative determination of the interaction between epinephrine and various insulin releasers in man. Diabetes *48*:946–54, 1978.
24. Goodner, C. J., and Porte, D., Jr.: Determinants of basal insulin secretion in man. *In* Handbook of Physiology, Endocrinology 1. Greep, R. O., Ed. Baltimore, American Physiological Association, 1972, pp. 597–609.
25. Rizza, R., Haymond, M., Cryer, P., and Gerich, J.: Differential effects of epinephrine on glucose production and disposal in man. Am. J. Physiol. *237*:E356–62, 1979.
26. Eigler, N., Sacca, L., and Sherwin, R.: Synergistic interactions of physiologic increments of glucagon, epinephrine and cortisol in the dog. J. Clin. Invest. *63*:114–23, 1979.