The Effect of Norepinephrine on Insulin Secretion and Glucose Effectiveness in Non–Insulin-Dependent Diabetes

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It has previously been shown that in normal subjects, physiological elevation of norepinephrine (NE) impairs insulin sensitivity (Si) but does not influence insulin secretion. The aim of this study was to determine the effect of short-term physiological elevation of NE on insulin secretion, Si, and glucose-mediated glucose disposal, or the glucose effectiveness index (Sg), in non–insulin-dependent diabetes mellitus (NIDDM). Two intravenous glucose tolerance tests (IVGTTs) were performed in eight well-controlled NIDDM patients, using a supplemental exogenous insulin infusion to achieve an approximation of normal endogenous insulin secretion. The IVGTTs were performed in random order after 30 minutes of either the saline (SAL) or NE (25 ng/kg/min) infusions, which were continued throughout the 3-hour IVGTT. Sg and Si were estimated by minimal model analysis of the IVGTT data as previously described. Plasma C-peptide was used to estimate insulin secretion rate using the ISEC program. NE infusion produced approximately a threefold increase in plasma NE, associated with (1) a significant reduction in glucose disposal ([K_G] SAL *v* NE, 0.73 ± 0.06 *v* 0.61 ± 0.06 × $10^{-2} \cdot min^{-1}$, $P < .05$), (2) no reduction in Si (2.33 ± 0.8 *v* 2.62 ± 0.9 × $10^{-4} \cdot min^{-1}$/mU/L, NS), (3) a reduced mean second-phase insulin secretion rate (1.21 ± 0.19 *v* 1.01 ± 0.16 × 10^{-3} pmol/kg/min per mmol/L glucose, $P < .05$), (4) a significant increase in Sg (0.89 ± 0.08 *v* 1.63 ± 0.2 × $10^{-2} \cdot min^{-1}$, $P < .05$), and (5) a corresponding increase in glucose effectiveness at zero insulin ([GEZI] 0.55 ± 0.13 *v* 1.30 ± 0.33 × $10^{-2} \cdot min^{-1}$, $P < .05$). These results show that in contrast to normal subjects, physiological elevation of NE in NIDDM does not result in a reduction in Si, but causes a reduction in glucose disposal related to inhibition of insulin secretion that is only partially compensated for by increased Sg.

THERE IS EVIDENCE that the adrenergic neuroendocrine system may play a part in the development of insulin resistance[1] and that molecular abnormalities of the β_3-adrenoceptor may lead to obesity[2] and an increased risk of non–insulin-dependent diabetes mellitus (NIDDM). However, in established NIDDM, the prime concern in disease management is to achieve good control of plasma glucose and prevent complications, and findings from the comprehensive Diabetes Control and Complications Trial underscore the importance of strict control in insulin-dependent diabetes mellitus (IDDM),[3] which may apply equally to NIDDM patients.[4] Plasma glucose homeostasis may be adversely affected by several perturbed states, such as stress related to physical exercise,[5] surgery,[6] thyroid disease,[7] and Cushing's disease.[8] The effects on mechanisms affecting diabetic control of stress such as that experienced in myocardial infarction, traumatic surgery, and similar moderate stress situations have not yet been fully elucidated.

The effects of the stress hormone epinephrine (EPI) on glucose metabolism in IDDM have been well documented[9-11]; significant impairment of glucose tolerance related to short-term EPI infusion in IDDM, for instance, is associated with a profound decrease in insulin sensitivity without affecting non–insulin-mediated glucose disposal.[11] The responses of β- and α-cell function to EPI have been shown to be atypical in NIDDM compared with normal subjects, in that EPI in NIDDM inhibits the maximal acute insulin response (AIR) and has no consistent effect on the acute glucagon response (AGR), whereas EPI in normal subjects does not inhibit the maximal AIR and enhances the AGR.[12] Moreover, stress hormone studies in IDDM cannot be validly extrapolated to NIDDM because of the distinct genetic and pathophysiological backgrounds of the two disorders. For example, patients exhibiting the features of syndrome X[13,14]—insulin resistance, hypertension, hyperlipidemia, and obesity—have been reported to show atypical responses to stress hormones even before developing NIDDM. This effect is seen in low insulin responders[15] and Pima Indians,[16] suggesting both genetic and acquired defects.

However, in the past, the effect of norepinephrine (NE) on glucose homeostasis has been less clear. Our studies have shown that a physiological elevation of NE in normal subjects affects the acute disposal of an intravenous glucose load, significantly reducing glucose tolerance (K_G) and insulin sensitivity (Si) without changing first- and second-phase insulin secretion (Φ1 and Φ2) or glucose-mediated glucose disposal (glucose effectiveness [Sg]). Inhibition of Si by NE in normal subjects was accompanied by an initial elevation of basal nonesterified fatty acids (NEFAs), after which there was a profound decrease in NEFAs during the intravenous glucose tolerance test (IVGTT).[17] In NIDDM and obesity, basal plasma NE levels are low,[18] and there is enhanced pressor response to NE in NIDDM.[19] Comparison of the effect of an elevation in NE to a moderately high level in NIDDM versus normal subjects has shown that in addition to the heightened pressor response, there is a greatly increased glycemia in NIDDM, related mainly to hepatic glucose production.[20]

Nonetheless, it remains unclear as to which determinants of glucose tolerance are affected in response to stress in the NIDDM patient; in particular, what is the specific role of NE? This study was therefore initiated to define the pattern of response of Sg, Si, and insulin secretion to a moderate physiological elevation of NE, as would occur during stress such as surgery, in NIDDM subjects.

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SUBJECTS AND METHODS

Eight NIDDM patients were studied, four men and four women with a mean age of 46 years (range, 24 to 68), a mean weight of 75 kg (range, 57 to 106), and a body mass index of 19 to 37 kg/m^2 (mean, 28). The mean duration of diabetes was 13 ± 3 years, and all subjects were being treated with dietary restriction with or without oral hypoglycemic agents: six patients were taking sulfonylureas (gliclazide, glibenclamide, or tolbutamide), two of whom were also taking a biguanide (metformin), whereas two were managed on diet alone. Oral hypoglycemic agents were discontinued 48 hours before each study. Apart from one patient (a 38-year-old man who had presented with proliferative retinopathy for which he had laser treatment), no patients had other disorders or complications at the time of study. One 51-year-old woman with a history of hot flushes was being treated with hormone replacement therapy (daily estrogen plus intermittent norethisterone), and another 41-year-old woman with a history of mild hypertension was being treated with amiloride and potassium. No other patients were taking medications known to affect carbohydrate metabolism. One patient was a cigarette smoker; he did not discontinue smoking before the studies, but did not smoke on a study day. Liver and renal function tests were normal, as were hemoglobin A_{1c} values (7.8% ± 1.3%; normal, <6.6%). All patients provided informed written consent, and the studies were approved by the St. Vincent's Hospital Human Research Ethics Committee.

Protocol

Patients were admitted to the Metabolic Ward at 8 AM, and basal fasting blood samples were taken for determination of glucose, insulin, catecholamines, glucagon, NEFAs, and C-peptide. An infusion of NE was commenced at a rate of 25 ng/kg/min for 30 minutes before, and 3 hours during an IVGTT. Pulse rate and blood pressure were recorded at 15-minute intervals, and an electrocardiogram cardiac monitor was used throughout the NE infusion. In random order, an identical separate control study was performed in the same patients, using a saline (SAL) infusion instead of the NE infusion (Fig 1).

Pre-IVGTT

Two basal fasting blood samples were taken, and plasma levels of glucose, insulin, NEFA, EPI, NE, and C-peptide were measured immediately before NE or SAL infusion and at 10-minute intervals for 30 minutes (with multiple sampling for glucose and insulin), the last sample being taken just before the IVGTT.

IVGTT

A glucose bolus of 200 mg/kg (to a maximum of 27 mL 50% dextrose) was administered over 60 seconds at time 0, and blood samples were collected for plasma glucose and insulin measurements at −10, −1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, and 180 minutes. Incremental insulin was infused using a modification of the regimen we previously described[21] in IDDM patients to simulate the dynamic plasma free-insulin response seen in nondiabetics ie, phase 1 (5 to 7 minutes), 7 mU/kg/min; phase 2 (10 to 20 minutes), 1 mU/kg/min; phase 3 (20 to 50 minutes), 0.5 mU/kg/min; and "basal" insulin (50 to 180 minutes), 0.2 mU/kg/min. To address the possible influence of the dose of exogenous insulin on the measurement of Si, we delivered the same dose in both SAL and NE protocols, aiming to achieve insulin levels close to those of normal subjects in both studies. Blood was sampled during the IVGTT at −10, −1, 60, and 180 minutes for catecholamines, NEFAs, and C-peptide. NEFAs were also sampled at 30 and 60 minutes, C-peptide at 5, 10, 16, 30, 60, 90, and 120 minutes, and glucagon at −10, −1, 30, 60, and 90 minutes. Blood glucose levels were monitored at the bedside at intervals during the IVGTT, and basal insulin infusion was reduced to 0.1 mU/kg/min if blood glucose decreased to less than 6 mmol/L.

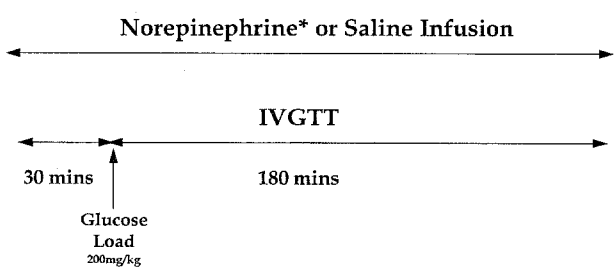

Fig 1. Study protocol. *25 ng/kg/min.

Analytical Techniques

Plasma glucose concentrations were measured with a Yellow Springs Instruments glucose analyzer (Yellow Springs, OH) using the glucose oxidase method. Plasma insulin and glucagon concentrations were measured by radioimmunoassay using charcoal separation of bound and free insulin according to the method of Albano et al.[22] With this assay, the normal fasting value is less than 10 mU/L, the sensitivity is less than 1 mU/L, and the interassay coefficient of variation is 6.3% at 10.5 mU/L and 8.4% at 22.0 mU/L. C-peptide was assayed with the Novo C-peptide radioimmunoassay kit (Novo Research Institute, Copenhagen, Denmark) using synthetic human C-peptide and guinea pig anti-human C-peptide antiserum, with a normal fasting range of 0.18 to 0.63 nmol/L. Plasma catecholamine levels were measured by a radioenzymatic assay kit (CAT-A-KIT; Amersham, Bucks, UK), and NEFAs were determined by an enzymatic colorimetric method using a kit (Wako Pure Chemical Industries, Osaka, Japan). In calculating the statistical significance of differences between mean values, planned single comparisons were made using conventional paired *t* tests.

Computer Modeling

A computer analysis of plasma insulin and glucose concentrations during the IVGTT was made using the minimal model for glucose kinetics of Bergman et al[23] and the simulation and modeling program CONSAM.[24] It had been impossible to analyze data from diabetic subjects using the original unmodified protocol, as the plasma insulin response was insufficient. We therefore established and validated a modification of the IVGTT protocol that can be analyzed by Bergman's minimal model of the IVGTT in diabetes[25] by infusing exogenous insulin to mimic the normal insulin secretion response. This approach enabled us to simultaneously estimate Sg and Si to assess the non–steady-state onset phase of insulin action, and a similar analysis was made in the present study.

The rate of glucose disappearance, referred to as the "absolute" K_G, was calculated as the least-square slope of the logarithm of the absolute plasma glucose concentration between 10 and 40 minutes after the glucose bolus, as previously described.[25] Similarly, the "incremental" K_G was calculated using glucose levels higher than basal. This estimation was made to compensate for any elevation of basal glucose levels pre-IVGTT associated with NE infusion, as previously seen in relation to EPI infusion, and also to allow an estimation of the proportion of K_G due to Sg, as previously described.[11]

To determine the rate of insulin secretion from C-peptide levels during the IVGTT, the ISEC insulin secretion program developed by Roman Hovorka* was used with the method reported by Van Cauter et al[26] in which C-peptide clearance rates are calculated from population studies that accommodate the variable factors of height, weight, sex,

*ISEC can be obtained from Roman Hovorka, PhD, Clinical Pharmacokinetics Department, Glaxo Group Research Ltd, Greenford Road, Greenford, Middlesex UB6 0HE, UK.

age, and condition classification (eg, normal, NIDDM, or obese). Endogenous insulin was estimated throughout the IVGTT from plasma C-peptide concentrations, based on C-peptide being an indirect physiological indicator of insulin secretion. Plasma concentrations of C-peptide at any specific time account for immediate and previous secretion, as it is a cumulative process. ISEC applies a constrained deconvolution method to isolate true insulin/C-peptide secretion from plasma concentrations.

RESULTS

Baseline

Plasma NE levels on admission to the ward were similar before the NE infusion and the control SAL infusion (201 ± 18 *v* 182 ± 20 ng/L). After 30 minutes' infusion of NE, the mean plasma NE increased to 657 ± 76 ng/L, whereas there was no change in the SAL control study after 30 minutes (196 ± 34 g/L). Plasma EPI levels showed no significant increase in either the NE or SAL study (Table 1). Plasma glucagon showed no consistent change during either study (Table 1). Baseline fasting C-peptide levels were similar in both studies (0.48 ± 0.09 *v* 0.45 ± 0.09 nmol/L). There was no significant elevation of basal plasma glucose in the 30 minutes pre-IVGTT during either infusion (SAL *v* NE, 8.4 ± 0.4 *v* 8.9 ± 0.4 mmol/L, $P > .05$; Fig 2B). However, there was a small nonsignificant increase in NEFAs during the first 30 minutes of the NE infusion study.

IVGTT

Plasma insulin profiles were similar in both infusions (Fig 2A), and plasma glucose levels (Fig 2B) showed that glucose tolerance was significantly decreased during the NE infusion compared with the SAL study (absolute K_G: SAL *v* NE, 0.73 ± 0.06 *v* 0.61 ± 0.06 × $10^{-2} \cdot min^{-1}$, $P < .05$; Fig 3B), similar to findings in normal subjects.[17] After reanalysis of the data to allow for any change in basal glucose levels during the 30-minute pre-IVGTT period, the incremental K_G was still significantly reduced (SAL *v* NE, 2.61 ± 0.39 *v* 2.31 ± 0.29 × $10^{-2} \cdot min^{-1}$, $P < .05$).

Computer analysis of IVGTT insulin and glucose data was successful and fully resolved in seven of eight cases. In one patient, the plasma insulin levels achieved were insufficient to allow adequate modeling, possibly because of an increased plasma clearance of insulin. In contrast to the normal subjects,

Table 1. Mean Plasma Concentration of Glucose, Insulin, Glucagon, Catecholamines, and NEFAs Before and After 30 Minutes' Infusion of SAL or NE Before the IVGTT

	SAL		NE	
Parameter	Basal	Pre-IVGTT (postclamp)	Basal	Pre-IVGTT
Glucose (mmol/L)	8.7 ± 0.3	8.4 ± 0.4	8.9 ± 0.5	8.9 ± 0.4
Insulin (mU/L)	36.1 ± 10.4	22.6 ± 6.2	22.9 ± 6.64	18.6 ± 5.6
NE (ng/L)	182 ± 20	196 ± 34	201 ± 60	657 ± 76*
EPI (ng/L)	35 ± 5	26 ± 5	57 ± 21	39 ± 10
C-peptide (pmol/mL)	0.48 ± 0.09	0.49 ± 0.09	0.45 ± 0.09	0.47 ± 0.05
Glucagon (ng/L)	82 ± 12	86 ± 11	82 ± 14	81 ± 5
NEFA (mmol/L)	0.51 ± 0.14	0.48 ± 0.13	0.44 ± 0.07	0.62 ± 0.11

*$P < .05$.

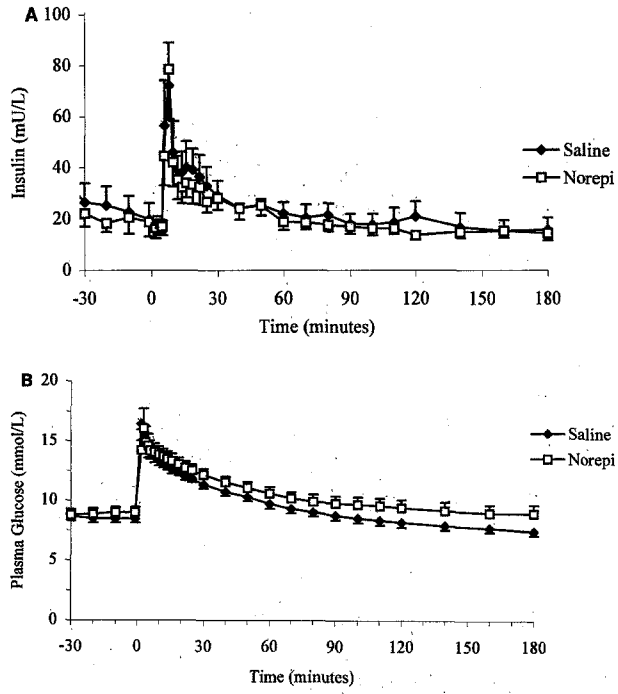

Fig 2. Plasma profiles before and during the IVGTT of insulin (A) and glucose (B) in 8 subjects with NIDDM during infusion of NE (□) and SA (◆), with exogenous insulin infused during the IVGTT according to the protocol.

the reduction in glucose disposal found during NE infusion was not associated with a significant decrease in Si in NIDDM patients (SAL *v* NE, 2.33 ± 0.8 *v* 2.62 ± 0.9 × $10^{-4} \cdot min^{-1}$/mU/L, NS; Fig 3B). However, there was a significant increase in Sg (SAL *v* NE, 0.89 ± 0.08 *v* 1.63 ± 0.2 × $10^{-2} \cdot$ min-1, $P < .05$; Fig 4A). To compensate for the small component of insulin action that is included in Sg estimation, glucose effectiveness at zero insulin (GEZI)[27] was also determined, calculated as the difference between total Sg and the basal insulin effect, which is a product of Si and basal insulin. A corresponding elevation in GEZI was observed in the NE study compared with the control study (SAL *v* NE, 0.55 ± 0.13 *v* 1.30 ± 0.33, $P < .05$; Fig 4B). NE infusion was associated with a significant increase in the percent of K_G ascribable to Sg, ie, Sg divided by incremental K_G (SAL *v* NE, 38% ± 5.0% *v* 73% ± 11.0%, $P < .05$).

Rate of Insulin Secretion

As expected in NIDDM patients, initial first-phase insulin secretion (between 0 and 10 minutes after glucose load) was low in both studies (Fig 5). During the second phase, mean endogenous insulin secretion was lower during NE versus SAL (Fig 5). This effect was quantified by calculating the average insulin secretion rate over 10 to 90 minutes, which was significantly decreased in the NE study (SAL *v* NE, 2.13 ± 0.36 *v* 1.82 ± 0.28 pmol/kg/min, $P = .04$). When insulin secretion was standardized for the glycemic stimulus induced by the IVGTT, the rate over 10 to 90 minutes (average insulin secretion/average plasma glucose) showed a uniform decrease in the NE study (SAL *v* NE, 1.21 ± 0.19 *v* 1.01 ± 0.016, $P = .01$; Fig 6).

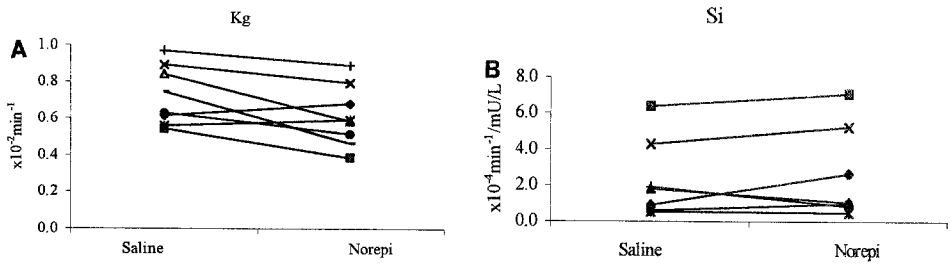

Fig 3. (A) Absolute K_G for 8 subjects during the IVGTT in the saline control and norepinephrine infusion studies. (B) Si estimated from computer analysis of the IVGTT during saline and norepinephrine studies in 7 subjects.

Correlations of Determinants of Glucose Disposal

In this study, there was no significant correlation between the reduction in glucose disappearance during the IVGTT in the NE study and the small increase in NEFA levels before the IVGTT. The change in NEFA levels was similar to but less marked than in normal nondiabetic subjects.[17] However, unlike normal subjects, there was no profound decrease in NEFAs during the 0- to 60-minute period of NE infusion in the NIDDM patients, possibly due to the lower rate of insulin secretion (Table 2).

DISCUSSION

This study shows that, as in nondiabetic subjects, acute glucose disposal is inhibited in NIDDM patients after infusion of NE at a level associated with moderate stress. Increased NE release in stress situations such as myocardial infarction, surgical trauma, and, indeed, excessive exercise or ketoacidosis, may directly affect glucose homeostasis.[17] There are undoubtedly several contributory factors, but the reasons for the excess mortality associated with diabetic patients following myocardial infarction have not been fully elucidated.[4] The metabolic changes that lead to impairment of myocardial function are related to the increased insulin resistance and hyperglycemia associated with an elevation of EPI and NE, among other factors.

The DIGAMI Study reported by Malmberg et al[28] indicated that in diabetics with acute myocardial infarction, infusion of insulin and glucose followed by a controlled insulin regimen was associated with decreased mortality over a 1-year period. However, rigorous control of plasma glucose in diabetic patients is difficult to achieve in stress situations. We have shown in the present study that when NE is elevated to a level similar to that found in situations of moderate stress, the role of insulin-mediated and non–insulin-mediated factors in glucose metabolism in patients with NIDDM may differ from that in normal subjects. In contrast to normal subjects, we found that a physiological elevation of NE did not result in decreased Si in NIDDM. Rather, the major finding in this study is that endogenous insulin secretion was significantly inhibited by NE in NIDDM, which does not occur in nondiabetic subjects. Whether this effect is related to the fact that β-cell function is already impaired in this group is not clear from our studies. It is also possible that "glucose toxicity" could sensitize the islet cells to NE suppression.

Recently, it has been appreciated that the interpretation of insulin secretion in the context of insulin sensitivity has been a subject that may be more complex than previously thought.[4,29,30] Moreover, in our studies, a reciprocal relationship between Si and insulin secretion was not seen, and there was in fact no significant change in Si in response to NE in NIDDM, although insulin secretion was reduced.

The NE infusion rate in this study was calculated to approximate the level of NE seen in conditions of moderate stress, and we found that no elevation of basal plasma glucose occurred during the basal 30-minute infusion, in contrast to the effect in normal subjects. It should be noted that a constant basal NE infusion was used, and a more prolonged infusion might have a significant effect on basal glucose levels in NIDDM patients. However, basal glucose levels with both SAL and NE are higher in NIDDM than in normal subjects, which led us to adapt our IVGTT protocol by using a smaller glucose bolus (200 mg/kg) to achieve peak glucose levels similar to those found in nondiabetics. It is possible that there is some protocol-related difference in the absolute results between normal and NIDDM subjects, but in our study NIDDM patients acted as their own control (in SAL studies), so the quantitative differences between the two protocols would not explain the difference in qualitative response to NE in the two groups.

An unexpected but significant increase in glucose-mediated glucose disposal (Sg) was associated with NE infusion. It is postulated that this increase partially compensates for the effect of low endogenous insulin secretion in reducing glucose tolerance in these patients. The role and significance of glucose effectiveness (Sg, defined as the influence of glucose at basal

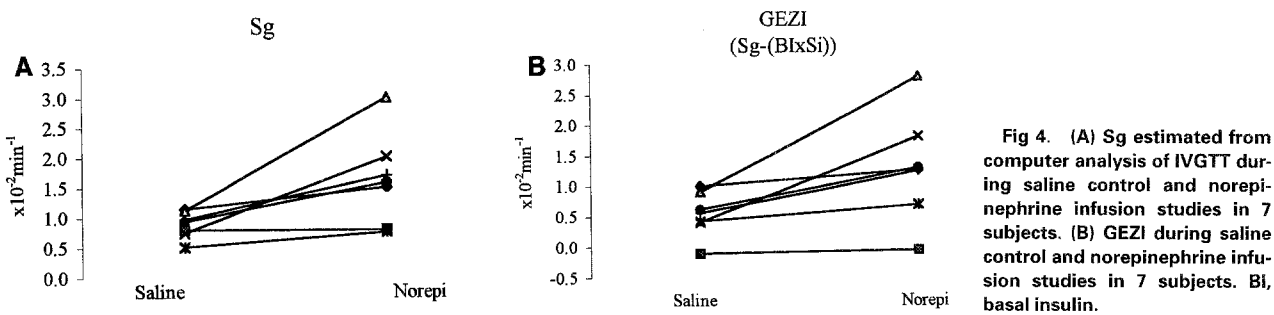

Fig 4. (A) Sg estimated from computer analysis of IVGTT during saline control and norepinephrine infusion studies in 7 subjects. (B) GEZI during saline control and norepinephrine infusion studies in 7 subjects. BI, basal insulin.

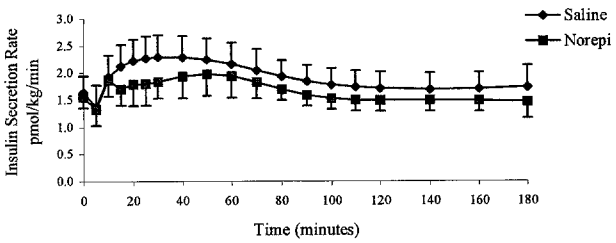

Fig 5. Endogenous insulin secretion rate during the IVGTT using the ISEC insulin secretion profile, computer-modeling C-peptide plasma concentrations over time in 8 subjects.

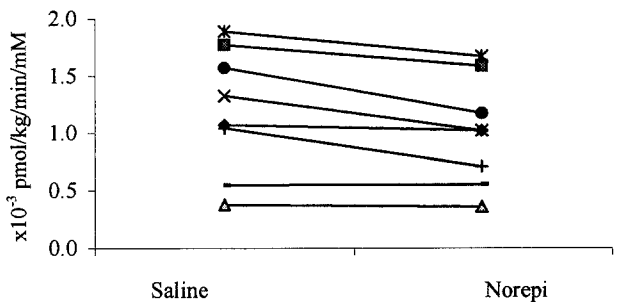

Fig 6. Second-phase endogenous insulin secretion, ie, the ratio of the average insulin secretion rate during the IVGTT to the average plasma glucose between 10 and 90 minutes following the glucose load.

insulin to enhance its own utilization and suppress its own endogenous production) in perturbed situations is increasingly recognized: it has been shown, for instance, that in nondiabetic subjects Sg is increased in acute exercise relative to normal resting situations, whereas Sg is low in anorexia nervosa, low-calorie dieting, and NIDDM.[31] A short-term physiological elevation of NE in normal subjects, while enhancing hepatic glucose production to a limited extent, has been shown to have no significant effect on Sg as such.[17,32] Similarly, short-term EPI infusion in IDDM results in a slight nonsignificant decrease in Sg,[11] and it may have been reasonable to expect that a similar lack of response to NE could occur in NIDDM, where Sg is already impaired.

However, non–insulin-mediated glucose disposal was enhanced in our NE study, as demonstrated by the significant increase in Sg associated with NE infusion in these insulin-resistant NIDDM patients and as reinforced by the increase in GEZI, obviating any effect related to the small amount of insulin action contained in the Sg measurement. This result (increased non–insulin-mediated glucose disposal) can be seen to act to some extent as a compensatory mechanism or counter-effect to the diminished insulin secretion in NIDDM patients when physiologically stressed, leading to a less profound inhibition of glucose tolerance in these patients.

One factor to be considered in explaining the differences in response to NE in normal and NIDDM patients might be related to effects on tissue blood flow. Increased cerebral blood flow in response to NE has been documented.[33] If this were associated with increased brain glucose uptake, it is feasible that the effects of NE on Sg in NIDDM would be mediated by altered cerebral blood flow. On the other hand, skeletal muscle is the major tissue for insulin-mediated glucose disposal, and changes in skeletal muscle blood flow are known to influence Si.[34] However, NE at the dose used in our studies has been shown to have no effect on skeletal muscle blood flow in normal subjects,[35] which may explain the lack of effect on Si. Increased plasma insulin has been shown to enhance skeletal muscle blood flow in normal subjects, but not in NIDDM patients.[36] Therefore, the lower insulin secretion rates seen in our NE studies may be associated with the decreased blood flow associated with NE, but this does not explain the increase in Sg that occurred.

A similar "compensatory" increase in Sg has recently been reported by Henriksen and members of our group in a collaborative study in nondiabetic, insulin-resistant first-degree relatives of NIDDM patients.[30] While increased Sg thus maintains glucose tolerance within normal limits in these normoinsulinemic NIDDM relatives, it might also represent a "stress-related" effect in prediabetics, as in our NIDDM patients.

An important goal would be to block the adverse effects on glucose homeostasis of unavoidable stressors in people with NIDDM, which demands elucidation of the underlying mechanisms. This study helps to clarify the role of a physiological elevation of NE in suppressing the already limited endogenous insulin secretion in NIDDM. The results of this study indicate that the decrease in glucose disposal after NE infusion in

Table 2. Mean Plasma Concentration of NEFAs, Glucagon, NE, and EPI During the IVGTT

	IVGTT (time after glucose bolus, min)				
Parameter	16	30	60	90	180
NEFA (mmol/L)					
SAL	0.44 ± 0.14	0.36 ± 0.13	0.28 ± 0.04	—	0.70 ± 0.15
NE	0.65 ± 0.10	0.51 ± 0.07	0.39 ± 0.06		0.85 ± 0.11
Glucagon (ng/L)					
SAL	—	60.3 ± 15.5	71.8 ± 17.8	58.9 ± 13.1	—
NE	—	76.1 ± 13.3	87.0 ± 17.9	92.7 ± 10.9	—
NE (ng/L)					
SAL	—	—	231 ± 31	—	247 ± 37
NE	—	—	678 ± 52*	—	687 ± 68*
EPI (ng/L)					
SAL	—	—	58 ± 14	—	60 ± 15
NE	—	—	58 ± 15	—	63 ± 14

*$P < .05$.

patients with NIDDM is attributable to a reduction in insulin secretion rather than inhibition of Si. It is also associated with increased Sg due to enhanced GEZI. If the compensatory effect of increased Sg could be further enhanced, the consequences of stress might be blunted, resulting in improved diabetes control and ultimately decreased morbidity. Further study to determine the cellular mechanisms for the compensatory increase of Sg may contribute to achievement of this goal.

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