Low-Dose Epinephrine Supports Plasma Glucose in Fasted Elderly Patients With Type 2 Diabetes

M.R. Burge, J.R. Kamin, C.T. Timm, C.R. Qualls, and D.S. Schade

Recent studies indicate that endogenous epinephrine provides protection against hypoglycemia in fasted elderly patients with type 2 diabetes treated with sulfonylureas. To establish a dose-response relationship and further characterize this hormonal action, 10 subjects with type 2 diabetes aged 67 ± 1.3 years and receiving glyburide 20 mg daily were studied on 3 separate occasions. Saline placebo, half dose epinephrine ([Epi] 0.375 μg/min), and full dose Epi (0.75 μg/min) were infused during the final 10 hours of a 28-hour fast in a paired, randomized single-blind study to simulate physiologic epinephrine levels. Substrate and hormonal parameters and glucose production (R_a), disposal (R_d), and metabolic clearance rates were determined every 30 minutes. In the placebo study, the mean decline in plasma glucose during the final 10 hours of fasting was −2.7 ± 0.6 mmol/L, compared with −0.3 ± 0.3 mmol/L in the half dose Epi study and an actual increase in glucose of 1.0 ± 0.8 mmol/L in the full dose Epi study ($P < .001$). There was a similar decline in the glucose R_a in all 3 studies, and the glucose R_d was not significantly different among the 3 study conditions. The baseline-adjusted metabolic clearance rate of glucose was significantly decreased during the epinephrine studies compared with the placebo study ($P = .01$). The concentration of other counterregulatory hormones did not differ between the studies. We conclude that low physiologic concentrations of epinephrine prevent the progressive decline in plasma glucose observed during fasting in elderly sulfonylurea-treated patients with type 2 diabetes. This finding may be attributable to a relative insulin resistance induced by epinephrine, resulting in a decreased rate of glucose clearance by cells.

ALTHOUGH HYPOGLYCEMIA has traditionally been an infrequent concern in patients with type 2 diabetes due to the limited efficacy of available therapeutic agents, the availability of potent new therapies to treat this disease increases the likelihood that hypoglycemia will occur more frequently in patients with type 2 diabetes. Thus, as in the case of type 1 diabetes, hypoglycemia is one of the principal barriers to the attainment of plasma glucose goals in patients with type 2 diabetes.

Recent data suggest that endogenous epinephrine secretion is the principal hormonal mechanism through which hypoglycemia is prevented among elderly sulfonylurea-treated patients with type 2 diabetes mellitus during a short-term fast. Specifically, none of 52 elderly subjects with type 2 diabetes who were receiving maximal doses of once-daily second-generation oral sulfonylurea agents (glyburide or glipizide Gastro-Intestinal Therapeutic System [GITS], 20 mg daily) developed hypoglycemia during a 23-hour fast.[1] Additionally, glucagon concentrations failed to increase during this study, and maintenance of glucose homeostasis was primarily attributed to the incremental secretion of endogenous epinephrine during conditions of normal or increased plasma glucose, with the mean plasma glucose concentration for the initiation of epinephrine secretion being 8.8 ± 2.8 mmol/L (158 ± 51 mg/dL). Such a hyperglycemic threshold for epinephrine secretion is markedly different from the situation in healthy nondiabetic subjects, who begin to exhibit increments in epinephrine secretion at plasma glucose levels between 2.3 and 3.8 mmol/L (41 and 68 mg/dL) and who secrete glucagon as the first defense against hypoglycemia.[2,3] However, elevated glucose concentrations for the initiation of epinephrine secretion have been reported in type 1 diabetes and have been correlated with poor glycemic control.[4]

Because counterregulatory hormonal mechanisms have not been well defined in type 2 diabetes, this study was performed to further characterize the role of epinephrine in protecting elderly fasted patients with type 2 diabetes against hypoglycemia during periods of endogenous hyperinsulinemia induced by oral sulfonylurea ingestion. We hypothesized that the exogenous infusion of low-physiologic increments of epinephrine would have measurable effects on glucose homeostasis in such patients. The results demonstrate a dose-response to the glucose homeostatic effects of exogenous epinephrine at low physiologic concentrations and suggest that epinephrine represents an important hormonal response to hypoglycemia in elderly patients with type 2 diabetes.

SUBJECTS AND METHODS

Subjects

Ten type 2 diabetic subjects receiving oral sulfonylurea therapy participated in a prospective randomized, single-blind, placebo-controlled crossover study. Inclusion criteria were type 2 diabetes treated with oral sulfonylureas alone for at least 2 months, age greater than 60 years, glycosylated hemoglobin concentration less than 12% (reference range, 4.8% to 7.8%), and body mass index (BMI) less than 38 kg/m^2. Patients were excluded from the study by the presence of severe cardiovascular, gastrointestinal, renal, or hepatic disease, concurrent medications that interfere with glucose homeostasis, malignancy, or substance abuse. All subjects provided written informed consent prior to the study as approved by the University of New Mexico Human Research Review Committee.

Protocol

The study protocol consisted of 3 28-hour fasting studies during which subjects received saline placebo, very–low-dose epinephrine, or

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low-dose epinephrine during the final 10 hours of the fast in random order. All subjects completed a standard exercise treadmill test prior to enrollment to exclude the presence of occult myocardial ischemia.[5] Upon study enrollment, all subjects were provided with a 30-day supply of glyburide (20 mg) and were instructed to take 1 tablet every morning upon awakening until completion of the study. All subjects used this dose of glyburide for at least 1 week prior to an overnight study, and 7 to 10 days separated each of the 3 overnight studies. Subjects were admitted to the University of New Mexico General Clinical Research Center at noon on the day before a fasting study, and forearm venous catheters were placed in each arm for administration of epinephrine or placebo and stable isotope (1 arm) and collection of arterialized blood samples (opposite arm). All subjects subsequently ingested a standard 8-kcal/kg meal according to the recommendations of the American Diabetes Association (50% carbohydrate, 20% protein, and 30% fat) at 2 PM.[6] No further caloric intake was allowed until completion of the 28-hour fast at 6 PM the following day. The daily dose of glyburide 20 mg was administered at 8:00 AM on the day of study, and data were collected over the subsequent 10 hours (18 to 28 hours of fasting). All subjects were allowed free access to noncaloric beverages during the fasting period, and all subjects drank a single caffeinated beverage (coffee or diet cola) at 8:00 AM on the morning of the fast.

All subjects completed 3 28-hour fasting studies during which each of the following treatments were administered in random order during the final 10 hours of the fast: (1) 0.45 mol/L saline (placebo study), (2) epinephrine 0.375 μg/min (half dose Epi study), and (3) epinephrine 0.75 μg/min (full dose Epi study). Upon completion of the protocol, 5 of the subjects participated in an optional fourth study during which 0.188 μg/min epinephrine was infused (quarter dose Epi study) under identical study conditions. Epinephrine infusions were prepared by mixing 1 mg epinephrine 1:1,000 in 0.45 mol/L saline to a final concentration of 1 μg/mL. Ascorbic acid 500 mg was added to each infusion to prevent oxidation of the epinephrine, and the epinephrine was protected from photodegradation by covering all infusion bags with a foil shield that was impervious to UV light as previously described.[7] All infusion rates were ramped so that the subjects received 1 third of the target dose during the first hour, 2 thirds of the target dose during the second hour, and the full target dose for the final 8 hours of the study. Blood was collected at 7:50 and 8:00 AM for baseline determinations, and then every 30 minutes for the remainder of the 10-hour study for determination of plasma glucose, total serum insulin, C-peptide, epinephrine, norepinephrine, glucagon, nonesterified fatty acids (NEFAs), and glucose turnover. Additionally, blood was sampled hourly for determination of cortisol and growth hormone concentrations. Systemic blood pressure and heart rate were determined using automated monitors every 30 minutes during the study. All subjects completed a 40-item hypoglycemia symptom questionnaire at baseline and every 2 hours during the study, rating symptoms such as fatigue, hunger, nervousness, weakness, tremor, sweating, tachycardia, dyspnea, and difficulty concentrating on a scale of 1 (no symptoms) to 7 (severe symptoms). Integrated neurocognitive function and attention were assessed with the Stroop Color-Word Test at baseline and every 2 hours during the study as previously described.[8]

Sample Analyses

Plasma glucose concentrations were determined with the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma was separated from blood elements by centrifugation immediately after sampling and frozen at −20°C for later determination, unless capillary blood glucose values were less than 4.4 mmol/L (80 mg/dL), at which time plasma glucose levels were determined immediately. Serum insulin concentrations were determined using the Coat-a-Count Insulin radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). C-peptide concentrations were determined using a radioimmunoassay (Incstar, Stillwater, MN). NEFA concentrations were determined enzymatically using a Wako kit (Wako Chemical, Dallas, TX) adapted to the Cobas-Bio instrument (Roche Instruments, Sommerville, NJ). Serum glucagon concentrations were determined by the core laboratory at Washington University (St Louis, MO) using a radioimmunoassay.[9] Samples for plasma epinephrine and norepinephrine were placed on ice immediately after sampling and stored at −70°C until needed for radioenzymatic assay.[10] Cortisol levels were determined by radioimmunoassay (Coat-a-Count; Diagnostic Products), as were growth hormone levels (Diagnostic Products).

Glucose turnover rates were determined using primed continuous infusions of the stable isotope D-2-glucose as previously described.[11] Briefly, D-2-glucose (Merck Isotopes, Montreal, Quebec, Canada) was infused at a mean rate of 13.6 ± 3.5 μg/kg/min after a mean priming dose of 82 ± 0.02 μg/kg/min for 10 minutes. Isotope infusions started 2 hours before study to ensure that isotopic equilibrium was attained. Isotopic enrichment of glucose was determined using gas chromatography–mass spectroscopy methodology as previously described,[12] and the rates of glucose appearance (R_a) and disposal (R_d) were calculated using non–steady-state assumptions with the Steele equation.[13] Glucose clearance was calculated as previously described.[14]

Statistical Analysis

All substrate and hormone variables were compared for an effect of treatment group (placebo *v* half dose Epi *v* full dose Epi) with a repeated-measures ANOVA and post hoc pairwise comparison, when appropriate, using SAS (SAS Institute, Cary, NC). For the overall ANOVA, the area under the curve from baseline was used as a summary measure for all variables according to the trapezoidal rule. For the post hoc pairwise analyses, data were summarized according to the following study time intervals to facilitate interpretation of the observed differences: baseline (mean of 7:50 and 8:00 AM samples), study hours 1 and 2 (period during which epinephrine infusion rates were increased), study hours 3 to 6, and study hours 7 to 10. Scores obtained from the Stroop Color-Word Test were analyzed in a similar manner. Hypoglycemia symptom scores were summarized as baseline-corrected peak values and compared using a repeated-measures ANOVA.

RESULTS

Baseline and descriptive characteristics of the study participants are summarized in Table 1.

Plasma Epinephrine

Repeated-measures ANOVA showed a statistically significant difference between the study groups with respect to epinephrine concentrations ($P < .001$; Fig 1A). Post hoc pairwise analysis showed no difference between the groups for baseline epinephrine concentrations, but a stepwise dose-dependent increase in the mean epinephrine was demonstrated between the placebo study and the half dose and full dose Epi studies ($P < .002$), as well as between the half dose and full dose Epi studies for all remaining time intervals ($P < .001$).

Table 1. Baseline and Descriptive Characteristics of the Study Participants

Characteristic	Mean ± SD
Age (yr)	67.7 ± 4.4
Sex ratio (male:female)	7:3
Duration of diabetes (yr)	5.9 ± 2.6
Glycosylated hemoglobin (reference range, 4.8%-7.8%)	8.0 ± 1.4
BMI (kg/m²)	28.7 ± 4.2

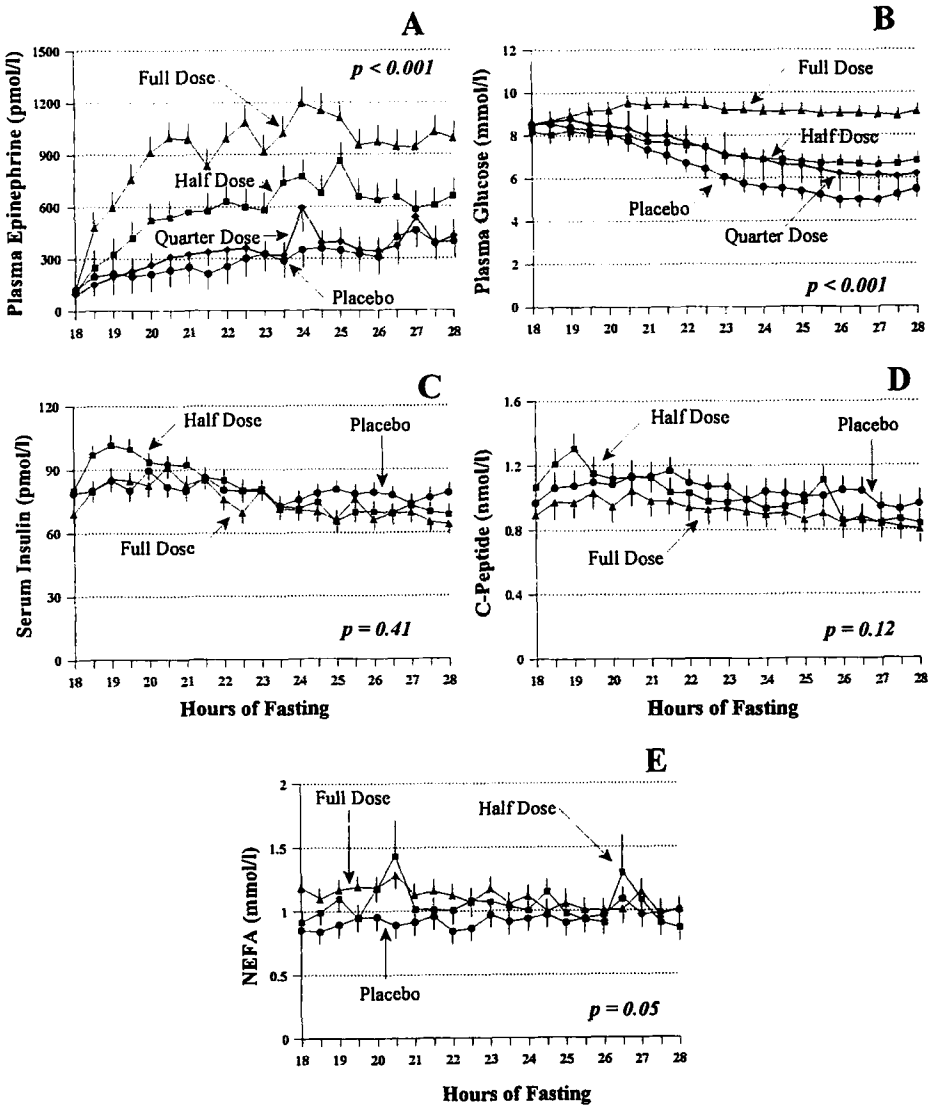

Fig 1. Plasma epinephrine (A), plasma glucose (B), total serum insulin (C), C-peptide (D), and NEFA (E) during the final 10 hours of a 28-hour fast among 10 elderly subjects with type 2 diabetes receiving glyburide 20 mg daily. ●, Placebo study; ■, half dose Epi study (0.375 μg/min); ▲, full dose Epi study (0.75 μg/min); ◆, quarter dose Epi study. *P* values reflect results of the repeated-measures ANOVA. To convert epinephrine concentrations to pg/mL, divide by 5.458.

Peak epinephrine concentrations of 680 ± 210 pmol/L and 1,030 ± 340 pmol/L were achieved in the half dose and full dose Epi studies, respectively. Finally, it is noteworthy that epinephrine concentrations increased during the placebo phase of the study, with the levels becoming significantly elevated above baseline after 24 hours of fasting and remaining elevated for the last 4 hours of the study (baseline *v* end of study, 124 ± 56 *v* 397 ± 301 pmol/L, $P = .01$) (Table 2).

Plasma Glucose

Plasma glucose concentrations differed according to the study condition on repeated-measures ANOVA ($P < .001$; Fig 1B). Post hoc pairwise analysis showed that mean plasma glucose concentrations were increased in the full dose Epi study compared with the placebo and half dose Epi studies during hours 3 to 6 of the fasting study (Table 2). By hours 7 to 10 of the study, a stepwise dose-dependent increase in mean plasma glucose was apparent between the study groups (Table 2). No differences in plasma glucose were detected between the groups at baseline or during the first 2 hours of study. Plasma glucose concentrations were not significantly different during the optional quarter dose Epi study versus the placebo study or half dose Epi study (Fig 1B).

Insulin and C-Peptide

Figure 1C and D shows that serum concentrations of insulin and C-peptide did not differ between the 3 study conditions.

NEFA

NEFA concentrations were increased in the full dose Epi study during hours 1 to 2 and 3 to 6 compared with the placebo study (Fig 1E and Table 2). Baseline concentrations of NEFA did not differ between the groups, nor did the concentrations differ during hours 7 to 10 of study.

Other Counterregulatory Hormones

Norepinephrine, glucagon, cortisol, and growth hormone levels did not differ significantly between the study groups over

Table 2. Results of Post Hoc Analyses for Variables With Significant Differences Detected on Repeated-Measures ANOVA (mean ± SD)

Variable	Placebo	Half Dose Epi	Full Dose Epi
Plasma epinephrine (pmol/L)			
Baseline	120 ± 60	110 ± 70	120 ± 90
Hours 1-2	200 ± 200*	330 ± 160*	610 ± 300
Hours 3-6	270 ± 290*†	610 ± 200*	990 ± 340
Hours 7-10	360 ± 250*†	680 ± 210*	1,030 ± 340
Plasma glucose (mmol/L)			
Baseline	8.5 ± 1.8	8.2 ± 1.3	8.5 ± 1.6
Hours 1-2	8.49 ± 1.6	8.1 ± 1.3	8.9 ± 1.4
Hours 3-6	6.8 ± 1.2*	7.5 ± 1.2*	9.3 ± 1.3
Hours 7-10	5.3 ± 0.7*†	6.8 ± 1.5*	9.1 ± 1.5
NEFA (mmol/L)			
Baseline	0.85 ± 0.21	1.18 ± 0.51	1.18 ± 0.51
Hours 1-2	0.89 ± 0.23*	1.01 ± 0.32	1.15 ± 0.24
Hours 3-6	0.91 ± 0.21*	1.09 ± 0.34	1.14 ± 0.20
Hours 7-10	0.97 ± 0.18	1.01 ± 0.27	1.03 ± 0.22
Glucose clearance (mL/kg/min)			
Baseline	1.50 ± 0.45†	2.00 ± 0.60*	1.52 ± 0.27
Hours 1-2	1.56 ± 0.42	1.87 ± 0.51	1.44 ± 0.24
Hours 3-6	1.69 ± 0.49	1.71 ± 0.46	1.30 ± 0.21
Hours 7-10	1.99 ± 0.64*	1.72 ± 0.37*	1.19 ± 0.23
Heart rate (bpm)			
Baseline	68 ± 11	68 ± 13	67 ± 13
Hours 1-2	64 ± 8*†	68 ± 9	70 ± 11
Hours 3-6	65 ± 9*†	72 ± 11	73 ± 12
Hours 7-10	68 ± 9*†	73 ± 10	74 ± 11

*$P < .05$ *v* full dose Epi study.
†$P < .05$ *v* half dose Epi study.

the 10-hour study by repeated-measures ANOVA. Additionally, glucagon concentrations failed to significantly increase during the placebo phase of the study (baseline *v* end of study, 84.3 ± 16.3 *v* 90.9 ± 27.9 ng/L, $P = .21$) (Fig 2).

Glucose Turnover

Glucose production (R_a) declined steadily during the 10-hour study period, as did glucose disposal (R_d), but no statistically significant differences were demonstrated between these parameters according to the study condition (Fig 3A and B). The metabolic clearance rate of glucose increased progressively in the placebo study and declined in the 2 epinephrine studies. Glucose clearance was increased in the half dose study compared with the other 2 study conditions at baseline, and decreased in the full dose study compared with the other 2 study conditions during the final 4 hours of the study (Table 2). When corrected for the baseline difference, glucose clearance was reduced in both epinephrine studies compared with placebo (Fig 3C). Moreover, the difference between mean glucose production and disposal ($R_a - R_d$) increased in a stepwise dose-dependent fashion according to study group ($P < .001$; Table 2 and Fig 3D). Under conditions of the full dose Epi study, the mean $R_a - R_d$ difference is positive, explaining the small increase in plasma glucose observed during the full dose Epi study.

Hemodynamic Effects of Epinephrine Infusion

Systolic blood pressure was slightly increased at baseline during the half dose Epi study compared with the placebo study (132 ± 12 *v* 145 ± 16 mm Hg, respectively, $P = .02$), but no other differences in blood pressure were observed between the study conditions (Fig 4A). Heart rate was increased slightly in the 2 epinephrine infusion studies compared with placebo, but the half dose Epi study did not significantly differ from the full dose Epi study (Fig 4B and Table 2).

DISCUSSION

The hormonal responses to hypoglycemia among elderly patients with or without type 2 diabetes have not been defined under conditions of prolonged fasting, but there are data regarding the hormonal responses to hypoglycemia that occur during exogenous hyperinsulinemia. Meneilly et al[15] have shown that healthy nondiabetic elderly subjects have an impaired release of glucagon and epinephrine in response to insulin-induced hypoglycemia compared with healthy young individuals, while Marker et al[16] have demonstrated a slower recovery from hypoglycemia among healthy elderly subjects compared with healthy young individuals. This latter impairment was attributed to decreased insulin clearance, reduced glucagon secretion, and perhaps delayed epinephrine secretion among the elderly subjects. It is unclear whether these mild abnormalities of glucose counterregulation are compounded by the presence of diabetes in the elderly. Boden et al[17] observed no differences in the counterregulatory hormone response or glucose recovery rate of 10 subjects with type 2 diabetes who underwent insulin-induced hypoglycemia compared with an age-matched nondiabetic control group. In a similar study comparing the physiologic response to hypoglycemia between healthy elderly subjects and elderly subjects with type 2 diabetes during a stepped hypoglycemic clamp protocol, Me-

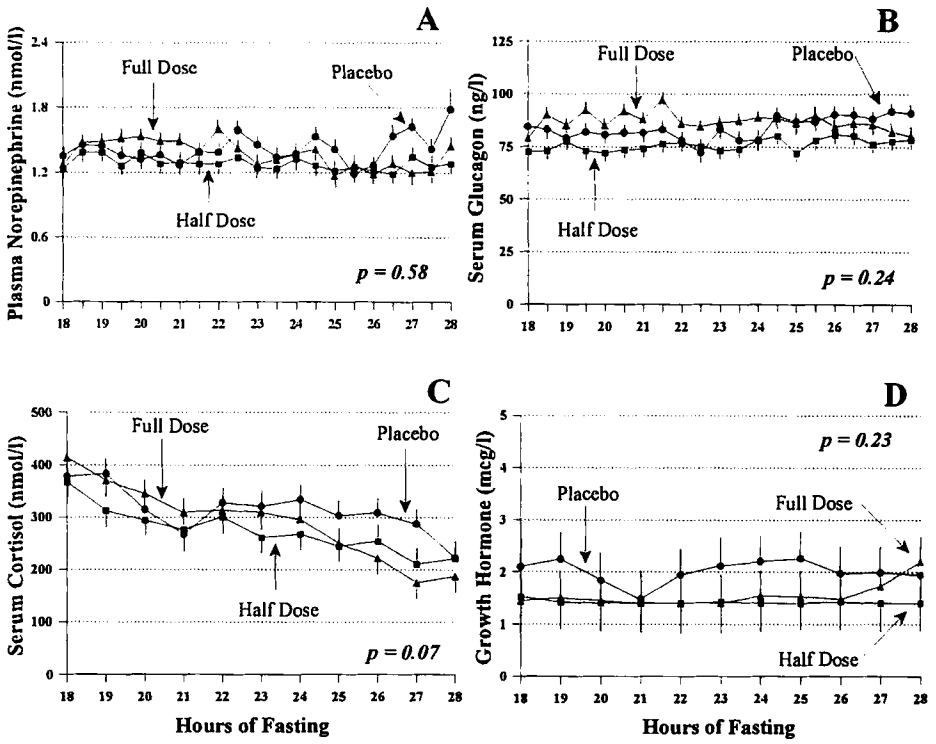

Fig 2. Plasma norepinephrine (A), serum glucagon (B), serum cortisol (C), and serum growth hormone (D) during the final 10 hours of a 28-hour fast among 10 elderly subjects with type 2 diabetes receiving glyburide 20 mg daily. ●, Placebo study; ■, half dose Epi study (0.375 μg/min); ▲, full dose Epi study (0.75 μg/min). *P* values reflect results of the repeated-measures ANOVA.

neilly et al[18] observed decreased glucagon secretion and increased epinephrine secretion in the group with diabetes. The results of these and other studies suggest that there is heterogeneity in the glucagon response to hypoglycemia among patients with type 2 diabetes and that, in some patients at least, epinephrine assumes a primary role in the response to hypoglycemia. Heterogeneity in the glucagon response to hypoglycemia may be attributable to numerous factors such as the duration of

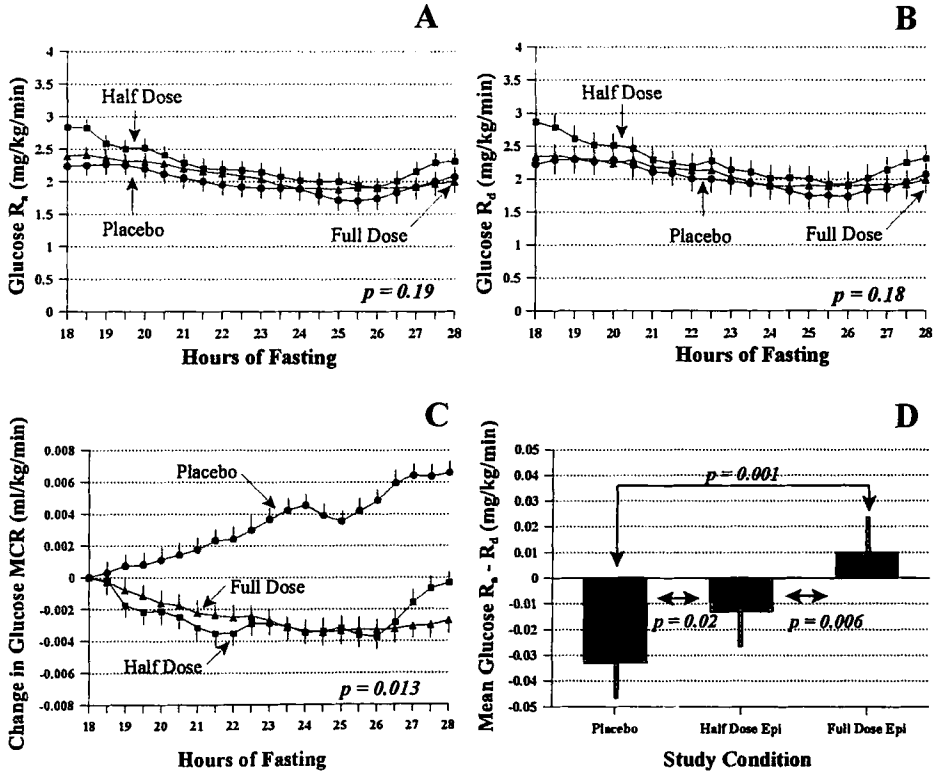

Fig 3. Glucose production (R_a, A) and disposal (R_d, B) rates and baseline-adjusted glucose metabolic clearance rate (MCR, C) during the final 10 hours of a 28-hour fast among 10 elderly subjects with type 2 diabetes receiving glyburide 20 mg daily. (D) Difference between mean R_a and R_d during all 3 study conditions. ●, Placebo study; ■, half dose Epi study (0.375 μg/min); ▲, full dose Epi study (0.75 μg/min). *P* values reflect results of the repeated-measures ANOVA.

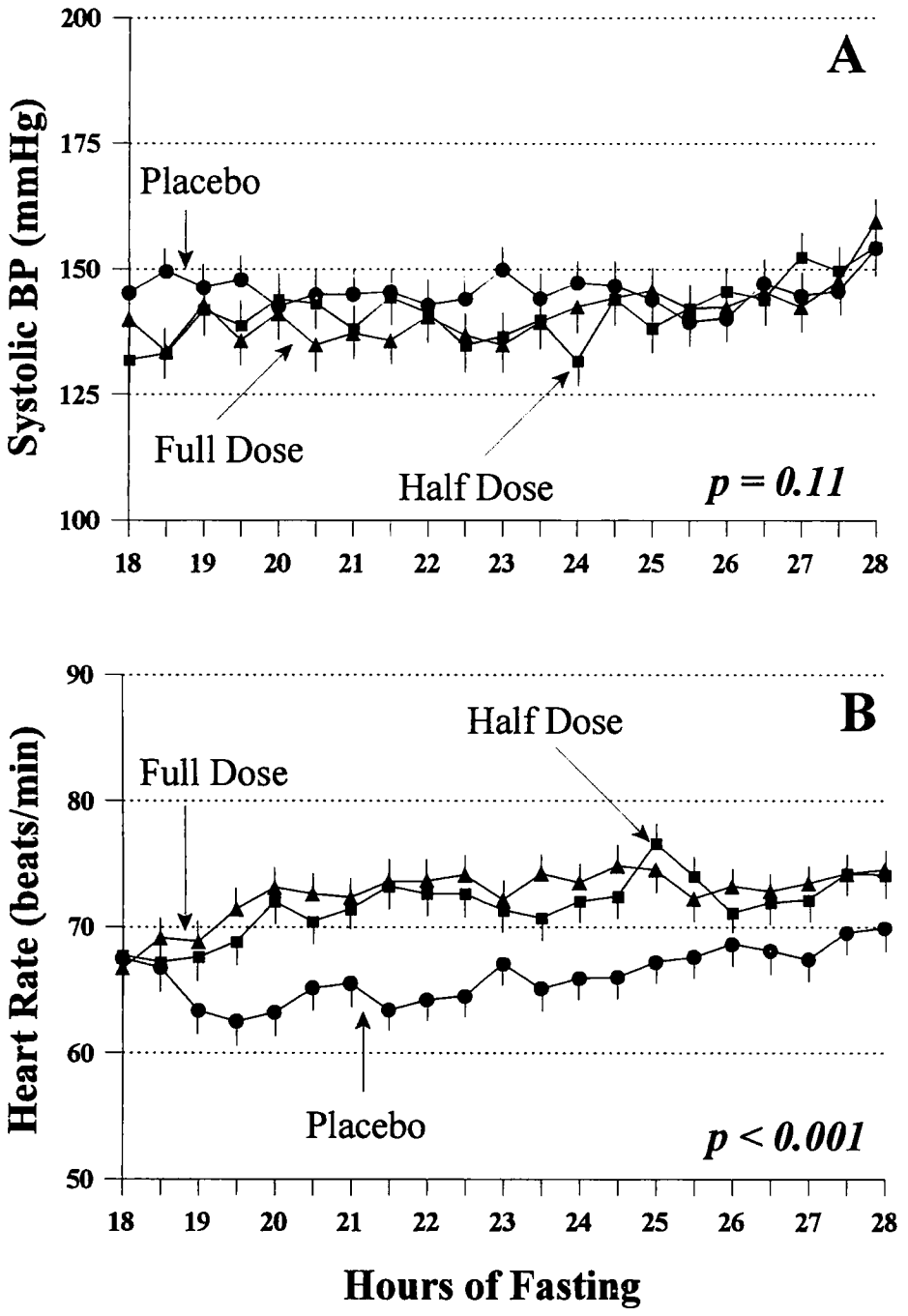

Fig 4. Systolic blood pressure (A) and heart rate (B) during the final 10 hours of a 28-hour fast among 10 elderly subjects with type 2 diabetes receiving glyburide 20 mg daily. ●, Placebo study; ■, half dose Epi study (0.375 μg/min); ▲, full dose Epi study (0.75 μg/min). *P* values reflect results of the repeated-measures ANOVA.

diabetes, the frequency of antecedent hypoglycemia, the severity of the hypoglycemic episode, and the degree of glycemic control.[1,19]

The current study demonstrates a dose-response of plasma glucose to exogenous epinephrine infusion among elderly fasted patients with type 2 diabetes treated with maximal doses of glyburide. These results are consistent with our previous observations and suggest that low physiologic concentrations of epinephrine may serve to maintain glucose homeostasis in elderly patients with type 2 diabetes during a short-term fast. The increase in endogenous epinephrine that occurred during the placebo studies supports this conclusion. Normal healthy humans typically exhibit epinephrine concentrations of 270 ± 160 pmol/L after 10 minutes of standing, and concentrations of 5,620 ± 5,840 pmol/L during insulin-induced hypoglycemia.[20] Thus, the epinephrine concentrations achieved in this study are within the normal physiologic range and are similar to the peak epinephrine concentrations of 570 ± 420 pmol/L observed among 52 elderly fasted patients with type 2 diabetes in our previous investigations.[1] Another epinephrine dose-response

study in normal healthy young individuals showed that plasma epinephrine concentrations of 818 to 1,092 pmol/L were necessary to effect increases in the plasma glucose concentration, while studies in type 1 diabetes have shown that these patients appear to have an enhanced responsiveness to the glycemic effects of epinephrine.[7,21,22] Whether such an increase in glucose responsiveness to epinephrine occurs in elderly subjects with type 2 diabetes is not known.

The failure to demonstrate incremental increases in glucose production or decreases in glucose disposal in this study to account for the observed increases in plasma glucose is problematic but not unique. In epinephrine dose-response studies in normal subjects, increased rates of glucose production occurred transiently during the first 60 minutes of epinephrine infusion and then returned to baseline.[7,23] It is possible that data were not collected frequently enough during this important interval in the current study to detect subtle increases in glucose production. Moreover, it is also possible that epinephrine masks changes in glucose turnover as determined by the Steele equation, as a consequence of a change in the volume of distribution for glucose (and accordingly, a change in glucose pool size) resulting from the vasodilatory effect of epinephrine on peripheral vasculature.[24] Regardless, the stepwise dose-dependent relationship between epinephrine levels and the difference between glucose production and disposal rates demonstrated in this study suggest that epinephrine affects both of these parameters as previously demonstrated.[25] Moreover, the demonstrated reduction in glucose clearance that occurred with epinephrine infusion in this study suggests that epinephrine induces a state of relative insulin resistance in tissues and is consistent with previous studies.[25] Studies with high-physiologic concentrations of epinephrine in healthy humans suggest that the suppression of glucose disposal may be the predominant glucose-sparing mechanism of this hormone.[23]

NEFA concentrations were elevated during full dose Epi infusion compared with placebo in this study. Recent reports suggest that insulin-induced decreases in hepatic glucose production may be only indirectly attributable to insulin itself and perhaps more directly related to declining NEFA availability as a result of insulin-induced suppression of lipolysis in adipose tissue.[26] Epinephrine is well documented to stimulate lipolysis and increase NEFA availability, and in fact, the lipolytic effects of epinephrine are more potent than its salutary effects on glucose production.[27] Interestingly, glucose production rates were weakly but positively correlated with NEFA concentrations in the current study ($r = .35$, $P = .002$).

In summary, this study demonstrates that elderly fasted sulfonylurea-treated patients with type 2 diabetes exhibit a dose-dependent hyperglycemic response to exogenously infused physiologic concentrations of epinephrine that may be encountered in vivo. These findings support the hypothesis that epinephrine is an important glucoregulatory response in elderly type 2 diabetic patients during a short-term fast.

REFERENCES

1. Burge MR, Schmitz-Fiorentino K, Fischette C, et al: A prospective trial of risk factors for sulfonylurea-induced hypoglycemia in type 2 diabetes mellitus. JAMA 279:137-143, 1998
2. Garber AJ, Cryer PE, Santiago JV, et al: The role of adrenergic mechanisms in the substrate and hormonal response to insulin-induced hypoglycemia in man. J Clin Invest 58:7-15, 1976
3. Mitrakou T, Ryan C, Veneman T, et al: Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Physiol 260:E67-E74, 1991
4. Boyle PJ, Schwartz NS, Shah SD, et al: Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and nondiabetics. N Engl J Med 318:1487-1492, 1988
5. The Committee on Exercise Testing: Guidelines for exercise testing: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 30:260-315, 1997
6. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus. Diabetes Care 20:S14-S17, 1997 (suppl 1)
7. Clutter WE, Bier DM, Shah SD, et al: Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J Clin Invest 66:94-101, 1980
8. Golden C: Stroop Color and Word Test. Chicago, IL, Stoelting, 1980
9. Ensinck JW: Immunoassays for glucagon, in Glucagon. Handbook of Experimental Pharmacology. New York, NY, Verlag, 1983, pp 203-221
10. Shah SD, Clutter WE, Cryer PE: External and internal standards in the single isotope derivative (radioenzymatic) assay of plasma norepinephrine and epinephrine in normal humans and persons with diabetes mellitus or chronic renal failure. J Lab Clin Med 106:624-629, 1985
11. Argoud GM, Schade DS, Eaton RP: Underestimation of hepatic glucose production by radioactive and stable tracers. Am J Physiol 252:E606-E615, 1987
12. Tserng K, Kalhan SC: Calculation of substrate turnover rate in stable isotope tracer studies. Am J Physiol 245:E308-E311, 1983
13. Steele R, Wall JS, De Bodo RC, et al: Measurement of size and turnover rate of body glucose pool by the isotope dilution method. Am J Physiol 187:15-24, 1956
14. Radziuk J, Lickley HLA: The metabolic clearance rate of glucose: Measurement and meaning. Diabetologia 28:315-322, 1985
15. Meneilly GS, Cheung E, Tuokko H: Altered responses to hypoglycemia of healthy elderly people. J Clin Endocrinol Metab 78:1341-1348, 1994
16. Marker JC, Cryer PE, Clutter WE: Attenuated glucose recovery from hypoglycemia in the elderly. Diabetes 41:671-678, 1992
17. Boden G, Soriano M, Hoeldke RD, et al: Counterregulatory hormone release and glucose recovery after hypoglycemia in non–insulin-dependent diabetic patients. Diabetes 32:1055-1059, 1983
18. Meneilly GS, Cheung E, Tuokko H: Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. Diabetes 43:403-410, 1994
19. Bolli GB, Tsalikian E, Haymond MW, et al: Defective glucose counterregulation after subcutaneous insulin in non–insulin-dependent diabetes mellitus. J Clin Invest 73:1532-1541, 1984
20. Cryer PE: Diseases of the sympathochromaffin system, in Felig P, Baxter JD, Frohman LA (eds): Endocrinology and Metabolism (ed 3). New York, NY, McGraw-Hill, 1995, pp 713-748
21. Shammon H, Hendler R, Sherwin RS: Altered responsiveness to

cortisol, epinephrine, and glucagon in insulin-infused juvenile-onset diabetics. Diabetes 29:284-291, 1980

22. Berk MA, Clutter WE, Skor D, et al: Enhanced glycemic responsiveness to epinephrine in insulin-dependent diabetes mellitus is the result of the inability to secrete insulin. J Clin Invest 75:1842-1851, 1985

23. Rizza RA, Haymond MW, Cryer PE, et al: Differential effects of physiologic concentrations of epinephrine on glucose production and disposal. Am J Physiol 237:E356-E362, 1979

24. Stratton JR, Pfeifer MA, Ritchie JL, et al: Hemodynamic effects of epinephrine: Concentration-effect study in humans. J Appl Physiol 58:1199-1206, 1985

25. Rizza RA, Cryer PE, Haymond MW, et al: Adrenergic mechanisms for the effect of epinephrine on glucose production and clearance in man. J Clin Invest 65:682-689, 1980

26. Bergman RN: New concepts in extracellular signaling for insulin action: The single gateway hypothesis. Recent Prog Horm Res 52:359-385, 1997

27. Galster AD, Clutter WE, Cryer PE, et al: Epinephrine plasma thresholds for lipolytic effects in man. J Clin Invest 67:1729-1738, 1981