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# Hypoglycemia and the sympathoadrenal system: neurogenic symptoms are largely the result of sympathetic neural, rather than adrenomedullary, activation

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**DeRosa, Michael A., and Philip E. Cryer.** Hypoglycemia and the sympathoadrenal system: neurogenic symptoms are largely the result of sympathetic neural, rather than adrenomedullary, activation. *Am J Physiol Endocrinol Metab* 287: E32–E41, 2004. First published February 17, 2004; 10.1152/ajpendo.00539.2003.—The relative contributions of the sympathetic nervous system and the adrenal medullae, the two components of the sympathoadrenal system, to the manifestations of hypoglycemia are largely unknown. We tested the hypothesis that the neurogenic symptoms of hypoglycemia are largely the result of sympathetic neural activation. To do so, we quantitated neurogenic symptoms, as well as norepinephrine (NE) kinetics and selected hemodynamic changes, during hyperinsulinemic euglycemic and stepped hypoglycemic clamps in 15 healthy control subjects (Controls) and four bilaterally adrenalectomized patients (ADX). Plasma epinephrine responses to hypoglycemia were virtually absent in ADX, as expected. Neurogenic symptom scores increased to higher values during the hypoglycemic compared with the euglycemic clamps in both Controls ($P < 0.0001$) (e.g., final scores of $7.8 \pm 1.2$ vs. $3.0 \pm 0.7$) and ADX ($P < 0.0001$) (e.g., final scores of $10.8 \pm 4.1$ vs. $2.5 \pm 1.0$). Plasma NE concentrations ($P < 0.0001$) and systemic NE spillover ($P = 0.0007$) increased during the hypoglycemic compared with the euglycemic clamps in Controls but not in ADX. Similarly, heart rate increased ($P = 0.0104$), diastolic blood pressure decreased ($P = 0.0003$), and forearm blood flow increased ($P < 0.0001$) during the hypoglycemic compared with the euglycemic clamps in Controls but not in ADX. These data indicate that the neurogenic symptoms of hypoglycemia are largely the result of sympathetic neural, rather than adrenomedullary, activation. They also suggest that the plasma NE and hemodynamic responses to hypoglycemia are largely the result of adrenomedullary, rather that sympathetic neural, activation.

adrenal medullae; norepinephrine; sympathetic nervous system; epinephrine

IN THE SETTING OF ENDOGENOUS INSULIN DEFICIENCY, relative or absolute therapeutic insulin excess, and absent glucagon responses to falling plasma glucose concentrations, reduced adrenomedullary epinephrine responses to a given level of hypoglycemia cause defective glucose counterregulation, and reduced sympathoadrenal responses cause hypoglycemia unawareness in type 1 diabetes mellitus and advanced type 2 diabetes mellitus (6, 7, 32). These two syndromes are the key components of hypoglycemia-associated autonomic failure, which is induced by recent antecedent hypoglycemia, and the resulting vicious cycle of recurrent iatrogenic hypoglycemia in people with diabetes (6, 7, 32).

Symptoms of hypoglycemia are classified as neuroglycopenic, the result of central nervous system glucose deprivation, and neurogenic (9, 36). Neurogenic, or autonomic, symptoms are the result of the perception of physiological changes caused by the central nervous system-mediated sympathoadrenal discharge triggered by hypoglycemia (36). They include both adrenergic symptoms, mediated by catecholamines released from sympathetic postganglionic neurons, the adrenal medullae, or both, and cholinergic symptoms mediated by acetylcholine released from sympathetic postganglionic neurons (36). The relative contributions of the sympathetic nervous system and of the adrenal medullae, the two components of the sympathoadrenal system, to the neurogenic symptoms, as well as to the increments in circulating norepinephrine and to the hemodynamic changes that occur during hypoglycemia, are largely unknown. It has been reported that the adrenergic symptom palpitation does not occur during hypoglycemia in adrenal-denervated individuals (13), implying an adrenomedullary origin of that symptom. The adrenergic symptom tremor has also been attributed to adrenomedullary activation, and the cholinergic symptom sweating is thought to be sympathetic neural in origin (3, 18).

The adrenal medullae are the source of biologically active plasma epinephrine concentrations (34). Epinephrine is a hormone in the classic sense. Norepinephrine is also released from the adrenal medullae (1, 4, 30); thus norepinephrine could function as a traditional hormone (35). However, under most conditions, circulating norepinephrine is derived largely from adrenergic sympathetic postganglionic neurons, and norepinephrine functions primarily as a neurotransmitter (35). Under resting conditions, the sympathetic nervous system has been estimated to be the source of 92–98% of circulating norepinephrine (1, 20, 30). Assumption of the upright position causes substantially greater increments in plasma norepinephrine than in plasma epinephrine, and adrenalectomized individuals have normal increments in plasma norepinephrine in response to standing (34), indicating a sympathetic neural origin of the increment in circulating norepinephrine. Hyperinsulinemia per se (plasma glucose held constant) raises plasma norepinephrine, but not epinephrine, concentrations and increases forearm norepinephrine spillover (27), again indicating a sympathetic neural origin of the increment in plasma norepinephrine. However, it cannot be assumed that increments in circulating norepinephrine are derived from sympathetic postganglionic

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neurons under all conditions. It has been estimated that the adrenal medullae contribute 30–45% of circulating norepinephrine in stressed animals (16). Hypoglycemia is a potent stimulus of adrenomedullary catecholamine secretion (32). It also stimulates sympathetic neural activity, as evidenced by increased muscle (8, 11, 20) and skin sudomotor (11) sympathetic nerve activity measured directly by microneurography and increased forearm norepinephrine spillover measured by isotope dilution (27, 28). On the basis of the finding that increased urinary norepinephrine during hypoglycemia was prevented by adrenalectomy in rodents, coupled with the absence of increased tissue norepinephrine turnover (an index of sympathetic neural activation) in hypoglycemic animals, Young and colleagues (37, 38) suggested that the adrenal medullae are the source of norepinephrine released in response to hypoglycemia. In healthy humans, plasma epinephrine and norepinephrine concentrations are not correlated when the subjects are in the supine and standing positions but are highly correlated ($r = 0.829$, $P < 0.001$) during hypoglycemia (5). The latter findings suggest disparate sources (i.e., the adrenal medullae and the sympathetic nervous system, respectively) of these circulating catecholamines under the former conditions but a common source (i.e., the adrenal medullae) during hypoglycemia. Finally, increments in the plasma norepinephrine concentration were not observed during hypoglycemia in adrenalectomized humans (14, 34). The hemodynamic responses to hypoglycemia, net vasodilation with increments in heart rate and cardiac output and widening of pulse pressure, have been attributed to increased adrenomedullary epinephrine secretion (in the context of the vasodilatory effect of the hyperinsulinemia used to produce the hypoglycemia) (19). Sympathetic neural activation may be a compensatory response that limits vasodilation and prevents hypotension (19).

On the basis of this background, we tested the hypothesis that the neurogenic symptoms of hypoglycemia are largely the result of sympathetic neural, rather than adrenomedullary, activation. We also sought further insight into the possibility that, although plasma norepinephrine is derived largely from sympathetic nerves during euglycemia, the plasma norepinephrine response to hypoglycemia is derived largely from the adrenal medullae and that the hemodynamic responses to hypoglycemia are largely the result of adrenomedullary, rather than sympathetic neural, activation. To do so, we quantitated neurogenic (and neuroglycopenic) symptoms (36); norepinephrine kinetics, including systemic and forearm norepinephrine spillover by [$^3$H]norepinephrine isotope dilution (25, 27, 28); and selected hemodynamic changes, including forearm blood flow by venous occlusion plethysmography (17) during hyperinsulinemic euglycemic and stepped hypoglycemic clamps in healthy subjects and in otherwise healthy, glucocorticoid- and mineralocorticoid-replaced, bilaterally adrenalectomized patients.

## METHODS

*Subjects.* Fifteen healthy control subjects [8 women and 7 men, with a mean (±SD) age of 25.3 ± 6.2 yr and a mean body mass index (BMI) of 23.4 ± 2.7 kg/m$^2$] and five otherwise healthy bilaterally adrenalectomized patients (4 women and 1 man, with a mean age of 40.8 ± 6.2 yr and a mean BMI of 25.9 ± 4.2 kg/m$^2$) gave their written consent to participate in this study, which was approved by the Washington University Medical Center Human Studies Committee (Institutional Review Board) and the Washington University Radioactive Drug Research Committee and was conducted at the Washington University General Clinical Research Center (GCRC). Inclusion criteria included normal hematocrits, fasting serum glucose concentrations, and serum creatinine concentrations. The adrenalectomized patients continued their usual glucocorticoid and mineralocorticoid replacement medications through the morning of each study. Cortisol (SoluCortef, Pharmacia and Upjohn, Kalamazoo, MI) was infused in a dose of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (25) through each study. Euglycemic clamps were performed in all five patients and hypoglycemic clamps in four patients.

*Protocol.* Healthy control subjects were studied as GCRC outpatients and adrenalectomized patients as GCRC inpatients. After an overnight fast, lines were inserted into an antecubital vein (for insulin and glucose infusions) and a hand vein (with that hand kept in an ~55°C box for arterialized venous sampling) and in a retrograde fashion into a deep antecubital vein (for forearm venous sampling). The participants remained in the supine position throughout. Hyperinsulinemic (2.0 $mU \cdot kg^{-1} \cdot min^{-1}$, 12.0 $pmol \cdot kg^{-1} \cdot min^{-1}$) euglycemic (~90 mg/dl, 5.0 mmol/l) clamps were performed on one occasion and, similarly, hyperinsulinemic-stepped hypoglycemic clamps (hourly steps of ~85, 75, 65, 55, and 45 mg/dl; ~4.7, 4.2, 3.6, 3.1, and 2.5 mmol/l) were performed on another occasion. Regular human insulin (Novolin R, Novo Nordisk, Baegsvard, Denmark) was infused throughout with variable infusions of 20% glucose based on plasma glucose measurements every 5 min to clamp plasma glucose concentrations at the target levels. Blood samples were drawn, and blood pressures and heart rates (Propaq Encore, Protocol Systems, Beaverton, OR) were recorded at 30-min intervals from −30 through 300 min. The electrocardiogram was monitored throughout.

*Symptoms.* Symptoms were quantitated by asking subjects to score (from 0, none, to 6, severe) each of 12 symptoms based on our published data (36); six neurogenic (adrenergic: heart pounding, shaky/tremulous, and nervous/anxious; cholinergic: sweaty, hungry, and tingling) and six neuroglycopenic (difficulty thinking/confused, tired/drowsy, weak, warm, faint, and dizzy) symptoms were assessed.

*Norepinephrine kinetics.* Tritiated norepinephrine (Levo[*ring*-2,5,6-$^3$H]norepinephrine, 40–80 Ci/mmol; Perkin Elmer Life Sciences-NEN, Boston, MA) was infused in a tracer dose of 10 $nCi \cdot kg^{-1} \cdot min^{-1}$ over the final 30 min of each of the five hourly glycemic steps during the hypoglycemic clamps and at the comparable time points during the euglycemic clamps. As described previously (25, 27, 28), norepinephrine kinetic parameters were calculated from data obtained from arterialized venous and deep forearm venous samples and from forearm blood flow measurements 20, 25, and 30 min into each [$^3$H]norepinephrine ([$^3$H]NE) infusion. [$^3$H]NE concentrations and NE specific activities were determined after organic extraction from plasma. The systemic (whole body) norepinephrine metabolic clearance rate (SNEMCR) and the systemic norepinephrine spillover (SNESO) rate were calculated as follows.

$$\text{SNEMCR (l/min)} = \frac{[^3\text{H}]\text{NE infusion rate (dpm/min)}}{[^3\text{H}]\text{NE concentration (dpm/l)}}$$

$$\text{SNESO (nmol/min)} = \frac{[^3\text{H}]\text{NE infusion rate (dpm/min)}}{\text{NE specific activity (dpm/nmol)}}$$

The forearm norepinephrine metabolic clearance rate (FNEMCR) and forearm norepinephrine spillover (FNESO) rate were calculated from forearm plasma flow (FPF = forearm blood flow × 1 − hematocrit) in milliliters per minute per 100 ml tissue and the forearm fractional extraction of norepinephrine ($F_{ex}$[$^3$H]NE)

$$F_{ex}[^3H]NE\ (unitless) = \frac{[^3H]NE_A - [^3H]NE_V}{[^3H]NE_A}$$

where A and V indicate arterialized venous and deep forearm venous values, respectively.

$$FNEMCR\ (ml \cdot min^{-1} \cdot 100\ ml\ tissue^{-1}) = F_{ex}[^3H]NE \times FPF$$

$$FENESO\ (nmol \cdot min^{-1} \cdot 100\ ml\ tissue^{-1}) = [(NE_V - NE_A) + (NE_A \times F_{ex}[^3H]NE)] \times FPF$$

We have documented previously that isotopic steady state is achieved well before the 20-, 25-, and 30-min sampling points during euglycemia (25, 27, 28) and hypoglycemia (27, 28), that forearm blood flows are stable at these measuring points during euglycemia and hypoglycemia (27, 28), and that oxygen tensions are low in the forearm deep venous samples (28).

*Forearm blood flow.* Forearm blood flow was measured by venous occlusion plethysmography (16) (Parks Medical Electronics, Aloha, OR) at the 20-, 25-, and 30-min time points during each [$^3$H]NE infusion. To exclude the hand from the measurement of blood flow, a wrist cuff was inflated to ~230 mmHg for 2 min before recordings and maintained during the recordings. Each blood flow value was the mean of five consecutive recordings.

*Analytical methods.* Plasma glucose was measured with a glucose oxidase method (YSI Analyzer 2, Yellow Springs Instruments, Yellow Springs, OH). Plasma epinephrine and norepinephrine were measured with a single isotope derivative (radioenzymatic) method (34), and insulin (23), C-peptide (23), glucagon (10), pancreatic polypeptide (15), growth hormone (31), and cortisol (12) were measured with radioimmunoassays. Serum nonesterified fatty acids (NEFA) were measured with an enzymatic colorimetric method (22), and blood lactate (24), β-hydroxybutyrate (29), and alanine (2) were measured with enzymatic techniques.

*Statistical methods.* Data are expressed as the means ± SE, except where the SD is specified. Data during the euglycemic and hypoglycemic clamps in each group (healthy control subjects and adrenalectomized patients) were analyzed by mixed-model repeated-measures analysis of variance. Condition-related (hypoglycemia vs. euglycemia) $P$ values are reported. $P$ values $<0.05$ were considered to indicate statistically significant differences.

## RESULTS

*Glucose, insulin, C-peptide, and glucose infusion rates.* The nominal plasma glucose concentration steps of 85, 75, 65, 55, and 45 mg/dl (4.7, 4.2, 3.6, 3.1, and 2.5 mmol/l) during the hypoglycemic clamps and the step of 90 mg/dl (5.0 mmol/l) during the euglycemic clamps were approximated in both the healthy control subjects and the adrenalectomized patients (Fig. 1). Plasma insulin concentrations were similar under both euglycemic and hypoglycemic conditions in both groups (Table 1). Plasma C-peptide concentrations were suppressed to a greater extent during the hypoglycemic compared with the euglycemic clamps in the healthy control subjects ($P < 0.0001$) and in the adrenalectomized patients ($P = 0.0013$) (Table 1). The glucose infusion rates required to maintain target plasma glucose concentrations were lower during the hypoglycemic than during the euglycemic clamps in the healthy control subjects ($P < 0.0001$) and in the adrenalectomized patients ($P = 0.0028$; Table 1).

*Epinephrine, glucagon, pancreatic polypeptide, growth hormone, and cortisol.* Arterialized venous plasma epinephrine concentrations increased from 19 ± 3 pg/ml (105 ± 15 pmol/l) at *time 0* to 515 ± 41 pg/ml (2,810 ± 223 pmol/l) at 300 min during the hypoglycemic clamps and were unchanged [−21 ± 3 pg/ml (115 ± 15 pmol/l) and 25 ± 2 pg/ml (135 ± 10 pmol/l), respectively] during the euglycemic clamps ($P < 0.0001$) in the healthy control subjects (Fig. 2). In contrast, there was virtually no epinephrine response to hypoglycemia in the adrenalectomized patients (Fig. 2). Plasma epinephrine concentrations appeared to increase slightly from 4 ± 3 pg/ml (20 ± 15 pmol/l) at *time 0* to 14 ± 8 pg/ml (75 ± 45 pmol/l) at 300 min, but epinephrine levels were not significantly different from those during the euglycemic clamps at 3 ± 1 pg/ml (15 ± 5 pmol/l) and 2 ± 1 pg/ml (10 ± 5 pmol/l), respectively. Plasma glucagon, pancreatic polypeptide, and growth hormone concentrations were significantly higher during the hypoglycemic clamps than during the euglycemic clamps in both the healthy control subjects ($P < 0.0001$ for all three hormones) and the adrenalectomized patients ($P < 0.0001$ for glucagon and pancreatic polypeptide, $P = 0.0028$ for growth hormone; Table 2). Plasma cortisol concentrations were significantly higher during the hypoglycemic clamps than during the euglycemic clamps in the healthy control subjects ($P < 0.0001$; Table 3). Cortisol replacement produced high physiological basal plasma cortisol concentrations in the adrenalectomized patients during both studies (Table 3).

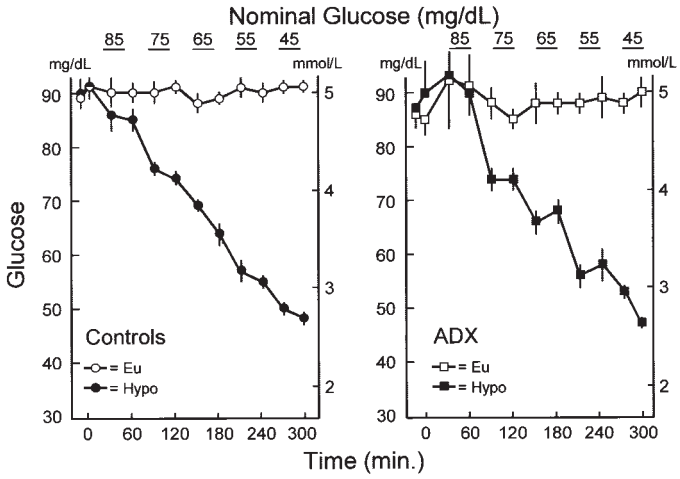


Fig. 1. Plasma glucose concentrations (means ± SE) during hyperinsulinemic stepped hypoglycemic clamps (Hypo, closed symbols) and euglycemic clamps (Eu, open symbols) in healthy control subjects (*left*) and bilaterally adrenalectomized patients (ADX, *right*).

*Lactate, NEFA, β-hydroxybutyrate, and alanine.* Blood lactate concentrations were higher during the hypoglycemic compared with the euglycemic clamps in the healthy control subjects ($P = 0.0002$) but were not different under the two conditions in the adrenalectomized patients (Table 4). Serum NEFA and blood β-hydroxybutyrate concentrations were suppressed comparably under hyperinsulinemic conditions in both groups (Table 4). Blood alanine concentrations did not differ under either condition in either group (data not shown).

*Neurogenic and neuroglycopenic symptoms.* Neurogenic symptom scores increased to higher values during the hypoglycemic compared with the euglycemic clamps in both the healthy control subjects ($P < 0.0001$) and the adrenalectomized patients ($P < 0.0001$; Fig. 3). The scores were 1.3 ± 0.5 at *time 0* and 7.8 ± 1.2 at 300 min during the hypoglycemic clamps compared with 0.4 ± 0.2 and 3.0 ± 0.7, respectively,

Table 1. *Plasma insulin and C-peptide concentrations and glucose infusion rates during Hypo clamps and Eu clamps in healthy control subjects and ADX patients*

| | Time, min | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | −15 | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 |
| Nominal glucose, mg/dl | | | | | | | | | | | | |
| Hypo | | 90 | 85 | 85 | 75 | 75 | 65 | 65 | 55 | 55 | 45 | 45 |
| Eu | | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 |
| Insulin, μU/ml | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo | 5±1 | 7±2 | 91±5 | 106±7 | 93±7 | 101±5 | 96±8 | 100±4 | 96±5 | 100±6 | 95±4 | 97±5 |
| Eu | 6±1 | 6±1 | 79±11 | 87±6 | 92±7 | 98±7 | 93±7 | 92±7 | 87±7 | 96±7 | 91±6 | 95±6 |
| ADX | | | | | | | | | | | | |
| Hypo | 7±2 | 5±1 | 88±17 | 102±10 | 99±15 | 95±11 | 101±10 | 102±16 | 113±19 | 113±15 | 118±14 | 124±16 |
| Eu | 5±1 | 4±1 | 112±16 | 117±15 | 115±11 | 120±14 | 116±12 | 115±14 | 115±11 | 113±14 | 108±14 | 116±24 |
| C-peptide, ng/ml | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo* | 1.4±0.1 | 1.4±0.1 | 1.1±0.1 | 0.8±0.1 | 0.7±0.1 | 0.5±0.0 | 0.4±0.0 | 0.4±0.0 | 0.3±0.0 | 0.2±0.0 | 0.2±0.0 | 0.2±0.0 |
| Eu | 1.4±0.1 | 1.4±0.1 | 1.2±0.2 | 1.0±0.1 | 0.9±0.1 | 0.9±0.1 | 0.9±0.1 | 0.8±0.1 | 0.9±0.1 | 0.8±0.1 | 0.9±0.1 | 1.0±0.1 |
| ADX | | | | | | | | | | | | |
| Hypo† | 2.2±0.4 | 2.1±0.3 | 1.7±0.3 | 1.4±0.3 | 0.9±0.2 | 0.7±0.1 | 0.6±0.1 | 0.5±0.1 | 0.5±0.1 | 0.4±0.1 | 0.3±0.1 | 0.3±0.1 |
| Eu | 2.4±0.1 | 2.5±0.3 | 1.7±0.2 | 1.4±0.2 | 1.2±0.2 | 1.0±0.2 | 1.2±0.2 | 1.1±0.2 | 1.2±0.2 | 1.1±0.1 | 1.0±0.2 | 1.0±0.2 |
| Glucose infusion rate, $mg \cdot kg^{-1} \cdot min^{-1}$ | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo‡ | | | 5.2±0.9 | 9.2±0.6 | 8.6±0.7 | 8.9±0.7 | 8.2±0.6 | 8.4±0.6 | 7.5±0.6 | 7.2±0.6 | 6.0±0.5 | 4.6±0.4 |
| Eu | | | 4.3±0.5 | 8.3±1.0 | 9.1±0.6 | 9.5±0.6 | 10.2±0.6 | 10.7±0.6 | 10.9±0.7 | 11.4±0.7 | 11.5±0.7 | 11.8±0.7 |
| ADX | | | | | | | | | | | | |
| Hypo§ | | | 4.0±0.7 | 6.4±1.3 | 5.5±1.6 | 5.8±0.6 | 5.8±0.4 | 6.0±0.2 | 5.3±0.6 | 5.7±0.8 | 4.1±0.8 | 3.2±0.8 |
| Eu | | | 4.2±0.8 | 4.6±1.6 | 6.0±1.5 | 6.7±1.6 | 7.2±1.4 | 8.0±1.9 | 8.4±1.6 | 8.2±1.2 | 8.6±1.3 | 8.3±1.3 |

Values are means ± SE. Hypo, hyperinsulinemic-stepped hypoglycemic; Eu, euglycemic; ADX, bilaterally adrenalectomized. To convert insulin to pmol/l, multiply μU/ml by 6.0. To convert C-peptide to nmol/l, multiply ng/ml by 0.331. To convert glucose infusion rate to $\mu mol \cdot kg^{-1} \cdot min^{-1}$, multiply $mg \cdot kg^{-1} \cdot min^{-1}$ by 5.551. *$P < 0.0001$; †$P = 0.0013$; ‡$P < 0.0001$; §$P = 0.0028$.

during the euglycemic clamps in the healthy control subjects. They were 0.3 ± 0.2 at *time 0* and 10.8 ± 4.1 at 300 min during the hypoglycemic clamps compared with 1.0 ± 0.9 and 2.5 ± 1.0, respectively, during the euglycemic clamps in the adrenalectomized patients. Comparisons of individual adrenergic and cholinergic neurogenic symptoms are shown in Fig. 4. Neuroglycopenic symptom scores were also higher during the hypoglycemic compared with the euglycemic clamps in both the healthy control subjects ($P = 0.0008$) and the adrenalectomized patients ($P < 0.0001$; Table 3).

*Norepinephrine, systemic norepinephrine spillover, and forearm norepinephrine spillover.* Arterialized venous plasma norepinephrine concentrations, averaged from samples at 50, 55, and 60 min of each glycemic step (20, 25, and 30 min into [$^3$H]NE infusions during the last 30 min of each glycemic step), increased to higher levels during the hypoglycemic compared with the euglycemic clamps in the healthy control subjects ($P < 0.0001$) but not in the adrenalectomized patients (Fig. 5). Similarly, systemic norepinephrine spillover rates increased to higher rates during the hypoglycemic compared with the euglycemic clamps in the healthy control subjects ($P = 0.0007$) but not in the adrenalectomized patients (Fig. 6). Forearm norepinephrine spillover also increased to higher rates during the hypoglycemic compared with the euglycemic clamps in the healthy control subjects ($P = 0.0339$) but not in the adrenalectomized patients (Fig. 7).

In the healthy control subjects, systemic norepinephrine metabolic clearance rates were 3.1 ± 0.2 l/min at baseline and 4.3 ± 0.5 l/min at the lowest glycemic step during the hypoglycemic clamps and were not significantly different ($P = 0.3148$) from those of 3.2 ± 0.3 and 3.8 ± 0.4 l/min, respectively, during the euglycemic clamps. In the adrenalectomized patients, the systemic norepinephrine metabolic clearance rates were 3.0 ± 0.6 l/min at baseline and 2.6 ± 0.5 l/min at the lowest glycemic step during the hypoglycemic clamps and were significantly ($P = 0.0126$) lower than those of 3.1 ± 0.7

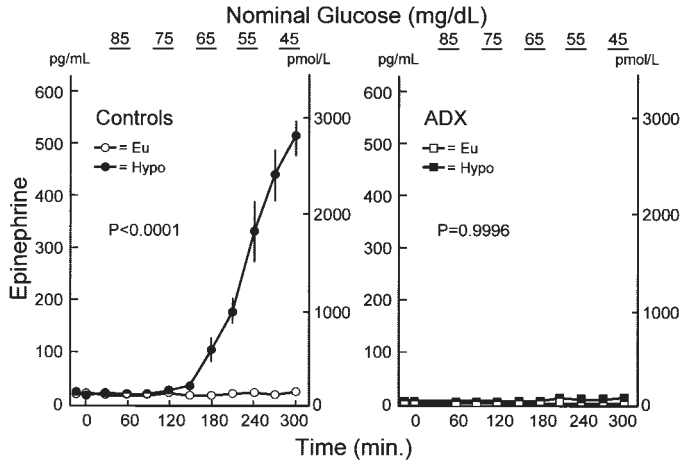


Fig. 2. Plasma epinephrine concentrations (means ± SE) during Hypo clamps (closed symbols) and Eu clamps (open symbols) in healthy control subjects (*left*) and ADX patients (*right*).

Table 2. *Plasma glucagon, pancreatic polypeptide, and growth hormone concentrations during Hypo and Eu clamps in healthy control subjects and ADX patients*

| | Time, min | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | −15 | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 |
| Nominal glucose, mg/dl | | | | | | | | | | | | |
| Hypo | | 90 | 85 | 85 | 75 | 75 | 65 | 65 | 55 | 55 | 45 | 45 |
| Eu | | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 |
| Glucagon, pg/ml | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo* | 61±6 | 64±6 | 55±5 | 50±6 | 54±7 | 53±7 | 54±8 | 61±8 | 72±15 | 78±12 | 83±15 | 76±12 |
| Eu | 61±6 | 56±4 | 47±4 | 49±5 | 46±5 | 45±5 | 47±6 | 44±5 | 44±5 | 42±5 | 42±5 | 42±5 |
| ADX | | | | | | | | | | | | |
| Hypo* | 92±6 | 86±8 | 80±11 | 74±11 | 72±13 | 75±12 | 79±9 | 73±10 | 87±12 | 89±11 | 94±16 | 107±16 |
| Eu | 84±10 | 86±8 | 76±8 | 70±10 | 68±10 | 67±8 | 67±10 | 67±12 | 66±10 | 61±10 | 68±13 | 64±12 |
| Pancreatic polypeptide, pg/ml | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo* | 87±10 | 92±14 | 73±7 | 64±6 | 65±6 | 65±7 | 73±7 | 125±25 | 168±44 | 450±87 | 588±114 | 617±115 |
| Eu | 104±16 | 97±14 | 84±10 | 72±9 | 77±12 | 71±7 | 71±9 | 64±7 | 70±10 | 67±7 | 71±10 | 76±14 |
| ADX | | | | | | | | | | | | |
| Hypo* | 139±24 | 127±18 | 96±11 | 92±10 | 91±17 | 92±11 | 124±37 | 111±14 | 351±72 | 505±154 | 939±257 | 1046±324 |
| Eu | 120±17 | 149±30 | 97±16 | 85±14 | 84±13 | 81±17 | 90±16 | 86±15 | 95±15 | 98±13 | 99±16 | 101±25 |
| Growth Hormone, ng/ml | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo* | 2.9±1.1 | 3.0±1.0 | 3.7±1.4 | 2.6±1.1 | 1.7±0.5 | 2.3±0.7 | 2.1±0.8 | 4.1±1.3 | 7.5±1.7 | 12.3±1.9 | 15.1±2.2 | 21.7±3.1 |
| Eu | 2.5±0.9 | 2.0±0.7 | 3.2±1.3 | 1.9±0.9 | 1.6±0.8 | 2.9±1.4 | 2.5±1.1 | 1.5±0.6 | 2.0±0.7 | 2.3±0.9 | 2.2±0.8 | 3.1±1.0 |
| ADX | | | | | | | | | | | | |
| Hypo† | 1.9±1.2 | 1.0±0.4 | 0.9±0.2 | 4.9±2.4 | 4.0±2.6 | 2.1±0.1 | 1.7±0.4 | 9.2±4.4 | 12.7±6.3 | 14.3±7.6 | 17.1±6.0 | 14.5±4.8 |
| Eu | 2.8±0.7 | 2.6±0.8 | 1.3±0.6 | 0.8±0.1 | 1.3±0.4 | 3.6±1.8 | 3.7±2.1 | 3.3±1.7 | 2.9±1.1 | 2.5±1.1 | 1.7±0.6 | 3.7±1.4 |

Values are means ± SE. To convert glucagon to pmol/l, multiply pg/ml by 0.2871. To convert pancreatic polypeptide to pmol/l, multiply pg/ml by 0.239. To convert growth hormone to pmol/l, multiply ng/ml by 44.15. *$P < 0.0001$; †$P = 0.0028$.

l/min and 4.4 ± 1.3 l/min, respectively, during the euglycemic clamps. In the healthy control subjects, forearm norepinephrine metabolic clearance rates were 0.5 ± 0.1 ml·min$^{-1}$·100 ml tissue$^{-1}$ at baseline and 1.1 ± 0.2 ml·min$^{-1}$·100 ml tissue$^{-1}$ at the lowest glycemic step during the hypoglycemic clamps and were not significantly different ($P = 0.2015$) from those of 0.5 ± 0.1 and 0.6 ± 0.2 ml·min$^{-1}$·100 ml tissue$^{-1}$, respectively, during the euglycemic clamps. In the adrenalectomized patients, the forearm norepinephrine metabolic clearance rates 0.5 ± 0.2 ml·min$^{-1}$·100 ml tissue$^{-1}$ at baseline and 0.2 ± 0.2 ml·min$^{-1}$·100 ml tissue$^{-1}$ at the lowest glycemic step during the hypoglycemic clamps are not significantly different ($P = 0.0892$) from those of 0.5 ± 0.1 and 0.6 ± 0.2 ml·min$^{-1}$·100 ml tissue$^{-1}$, respectively, during the euglycemic clamps.

*Heart rate, blood pressures, and forearm plasma flow.* Heart rate increased to a greater extent during the hypoglycemic compared with the euglycemic clamps in the healthy control subjects ($P = 0.0104$) but not in the adrenalectomized patients

Table 3. *Plasma cortisol concentrations and neuroglycopenic symptom scores during Hypo and Eu clamps in healthy control subjects and ADX patients*

| | Time, min | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | −15 | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 |
| Nominal glucose, mg/dl | | | | | | | | | | | | |
| Hypo | | 90 | 85 | 85 | 75 | 75 | 65 | 65 | 55 | 55 | 45 | 45 |
| Eu | | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 |
| Cortisol, μg/dl | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo* | 16.6±2.5 | 16.1±2.3 | 13.5±2.2 | 12.9±2.2 | 12.1±2.0 | 11.6±1.8 | 11.5±1.5 | 12.3±1.6 | 13.9±1.3 | 15.2±1.2 | 17.5±1.6 | 20.2±1.8 |
| Eu | 20.8±3.0 | 20.4±3.2 | 16.6±3.0 | 15.6±2.3 | 15.6±2.4 | 13.3±2.1 | 12.5±1.9 | 11.5±1.6 | 10.3±1.5 | 10.3±1.6 | 9.8±1.7 | 10.3±2.1 |
| ADX | | | | | | | | | | | | |
| Hypo | 26.2±7.5 | 32.7±5.7 | 28.3±2.9 | 22.1±0.4 | 21.3±1.5 | 21.2±0.6 | 20.2±2.3 | 20.8±3.1 | 18.1±3.3 | 17.0±3.2 | 17.8±3.1 | 17.0±0.8 |
| Eu | 25.2±5.1 | 27.4±5.3 | 31.6±5.2 | 25.0±3.2 | 23.9±3.0 | 24.0±2.4 | 22.2±2.2 | 23.3±3.3 | 21.1±2.1 | 20.6±2.0 | 19.7±3.8 | 18.5±3.6 |
| Neuroglycopenic symptom scores | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo† | 1.5±0.5 | 1.3±0.4 | 1.2±0.4 | 1.3±0.3 | 1.1±0.3 | 1.2±0.3 | 1.4±0.4 | 2.3±0.7 | 2.2±0.4 | 3.2±0.7 | 4.0±0.7 | 5.4±1.0 |
| Eu | 0.8±0.2 | 0.8±0.3 | 1.0±0.5 | 1.4±0.5 | 1.5±0.4 | 1.6±0.5 | 1.9±0.6 | 1.7±0.6 | 1.8±0.6 | 1.4±0.4 | 1.5±0.5 | 1.4±0.4 |
| ADX | | | | | | | | | | | | |
| Hypo* | 0.8±0.5 | 1.5±1.0 | 1.3±1.0 | 2.3±1.3 | 2.5±1.0 | 4.0±0.4 | 1.0±0.6 | 1.5±0.6 | 3.3±0.1 | 4.3±1.6 | 9.5±3.8 | 15.3±6.7 |
| Eu | 2.6±1.7 | 2.2±1.6 | 2.2±1.5 | 2.4±0.5 | 1.4±0.5 | 1.8±0.6 | 2.8±1.0 | 2.2±0.4 | 2.4±0.8 | 1.8±0.7 | 1.8±1.0 | 1.5±1.0 |

Values are means ± SE. To convert cortisol to nmol/l, multiply μg/dl by 27.59. *$P < 0.0001$; †$P = 0.0008$.

Table 4. *Blood lactate, serum NEFA, and blood β-hydroxybutyrate concentrations during Hypo and Eu clamps in healthy control subjects and ADX patients*

| | Time, min | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | −15 | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 |
| Nominal glucose, mg/dl | | | | | | | | | | | | |
| Hypo | | 90 | 85 | 85 | 75 | 75 | 65 | 65 | 55 | 55 | 45 | 45 |
| Eu | | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 |
| Lactate, mmol/l | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo* | 0.89±0.11 | 0.88±0.13 | 1.29±0.13 | 1.48±0.13 | 1.46±0.09 | 1.34±0.12 | 1.22±0.07 | 1.42±0.13 | 1.48±0.10 | 1.68±0.15 | 1.63±0.14 | 2.01±0.15 |
| Eu | 0.87±0.15 | 0.80±0.13 | 1.13±0.11 | 1.32±0.12 | 1.32±0.10 | 1.35±0.09 | 1.46±0.14 | 1.46±0.14 | 1.21±0.09 | 1.23±0.10 | 1.16±0.09 | 1.41±0.12 |
| ADX | | | | | | | | | | | | |
| Hypo | 1.09±0.13 | 0.93±0.14 | 1.22±0.22 | 1.50±0.14 | 1.43±0.17 | 1.66±0.12 | 1.28±0.09 | 1.08±0.14 | 1.09±0.08 | 0.99±0.09 | 0.97±0.12 | 0.94±0.09 |
| Eu | 1.10±0.12 | 1.07±0.08 | 1.12±0.18 | 1.30±0.14 | 1.41±0.17 | 1.28±0.16 | 1.15±0.16 | 1.23±0.14 | 1.34±0.13 | 1.37±0.11 | 1.38±0.10 | 1.39±0.16 |
| NEFA, μmol/l | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo | 372±42 | 396±35 | 129±16 | 73±9 | 70±9 | 66±8 | 54±7 | 53±8 | 48±7 | 50±8 | 58±11 | 62±13 |
| Eu | 478±42 | 463±36 | 186±38 | 89±13 | 74±11 | 65±10 | 58±10 | 53±9 | 46±7 | 49±9 | 51±8 | 51±7 |
| ADX | | | | | | | | | | | | |
| Hypo | 528±65 | 522±44 | 225±61 | 70±21 | 64±12 | 58±10 | 55±9 | 58±10 | 52±8 | 51±10 | 59±9 | 59±15 |
| Eu | 565±148 | 555±149 | 282±154 | 99±48 | 56±12 | 46±9 | 47±13 | 35±7 | 34±5 | 32±7 | 38±5 | 56±11 |
| β-Hydroxybutyrate, μmol/l | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo | 180±24 | 160±24 | 111±11 | 97±12 | 105±12 | 92±11 | 94±12 | 96±10 | 89±12 | 97±9 | 109±11 | 94±10 |
| Eu | 196±28 | 200±20 | 146±12 | 161±18 | 106±8 | 92±7 | 98±13 | 103±10 | 116±27 | 85±11 | 96±11 | 101±12 |
| ADX | | | | | | | | | | | | |
| Hypo | 141±16 | 125±29 | 85±18 | 50±20 | 88±12 | 79±20 | 89±11 | 90±23 | 91±21 | 84±10 | 106±6 | 113±19 |
| Eu | 507±241 | 510±241 | 436±239 | 205±75 | 141±38 | 82±26 | 78±21 | 99±17 | 135±22 | 108±23 | 102±21 | 134±33 |

Values are means ± SE. NEFA, nonesterified fatty acids. *$P = 0.0002$.

(Table 5). Systolic blood pressure did not differ significantly under either condition in either group (Table 5). Diastolic blood pressure decreased to a greater extent during the hypoglycemic compared with the euglycemic clamps in the healthy control subjects ($P = 0.0003$) but not in the adrenalectomized patients (Table 5). Forearm plasma flow increased to higher rates during the hypoglycemic compared with the euglycemic clamps on the healthy control subjects ($P < 0.0001$) but not in the adrenalectomized patients (Fig. 8).

## DISCUSSION

These data indicate that the neurogenic (autonomic) symptoms of hypoglycemia, both the adrenergic and the cholinergic neurogenic symptoms (36), are largely the result of sympathetic neural, rather than adrenomedullary, activation. They also suggest that, although circulating norepinephrine is derived largely from the sympathetic nervous system during euglycemia, the plasma norepinephrine response to hypoglycemia is derived largely from the adrenal medullae and that the

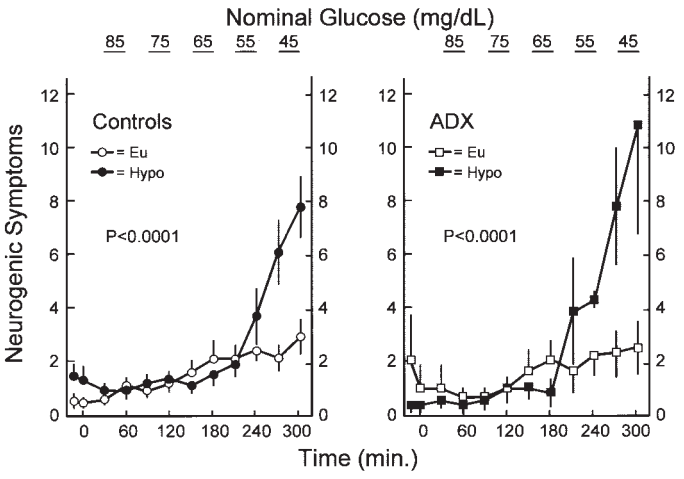


Fig. 3. Neurogenic symptom scores (means ± SE) during Hypo clamps (closed symbols) and Eu clamps (open symbols) in healthy control subjects (*left*) and ADX patients (*right*).

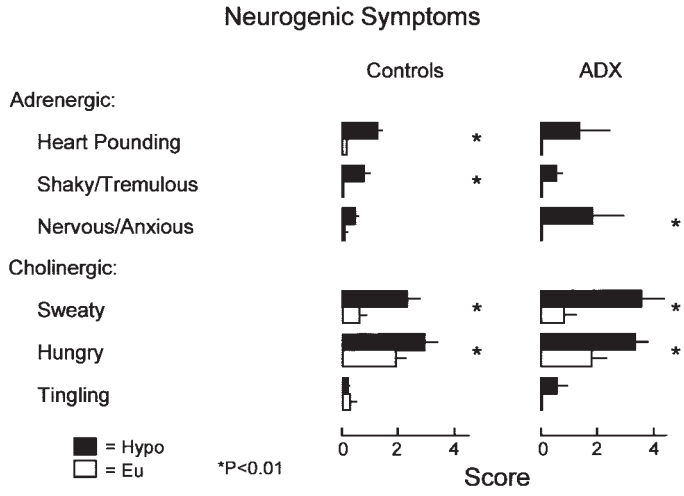


Fig. 4. Adrenergic and cholinergic neurogenic symptom scores (means ± SE) at end of Hypo clamps (closed bars) and Eu clamps (open bars) in healthy control subjects and ADX patients.

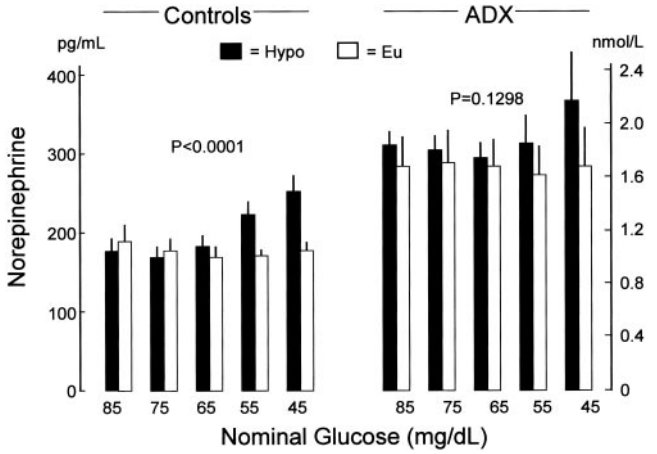


Fig. 5. Plasma norepinephrine concentrations (means ± SE) over the last 10 min of each 1-h Hypo clamp step (closed bars) and at the same time points during Eu clamps (open bars) in healthy control subjects (*left*) and ADX patients (*right*).

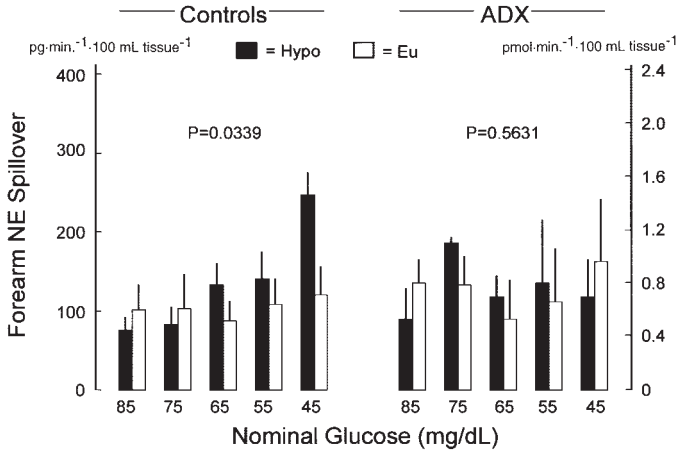


Fig. 7. Forearm norepinephrine (NE) spillover rates (means ± SE) over the last 10 min of each 1-h Hypo clamp step (closed bars) and at the same time points during Eu clamps (open bars) in healthy control subjects (*left*) and ADX patients (*right*).

hemodynamic responses to hypoglycemia are largely the result of adrenomedullary activation.

Typical neurogenic symptoms developed during hyperinsulinemic hypoglycemia, compared with hyperinsulinemic euglycemia, in individuals with intact adrenal medullae (as documented by their brisk plasma epinephrine response to hypoglycemia) and in individuals without adrenal medullae (as evidenced by their histories of bilateral adrenalectomy and documented by their virtual absence of a plasma epinephrine response to hypoglycemia). These neurogenic symptoms are the result of the perception of physiological changes caused by the central nervous system-mediated sympathoadrenal discharge triggered by hypoglycemia, as evidenced by the fact that they are reduced by administration of antagonists of the classical adrenergic neurotransmitters and hormones norepinephrine and epinephrine and of the classical cholinergic neurotransmitter acetylcholine (36). Therefore, it follows that the neurogenic symptoms of hypoglycemia must be largely the result of sympathetic neural, rather than adrenomedullary,

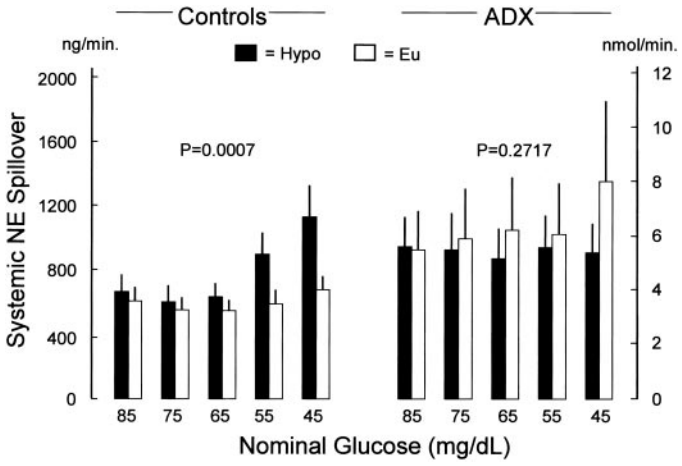


Fig. 6. Systemic norepinephrine spillover rates (means ± SE) over the last 10 min of each 1-h Hypo clamp step (closed bars) and at the same time points during Eu clamps (open bars) in healthy control subjects (*left*) and ADX patients (*right*).

activation by hypoglycemia. Although it is conceivable that adrenomedullary epinephrine, or some other adrenomedullary product, might contribute to the neurogenic symptoms of hypoglycemia, the present data provide no clues to that possibility. Each of the six individual neurogenic symptoms evaluated was either significantly more prominent (nervous/anxious, sweaty, hungry) or tended to be more prominent (heart pounding, shaky/tremulous, tingling) during hypoglycemia compared with euglycemia in the adrenalectomized patients despite the small sample size.

Consideration of the individual neurogenic symptoms assessed in the present study generally supports our earlier analysis of the adrenergic (catecholamine-mediated) and cholinergic (acetylcholine-mediated) symptoms of hypoglycemia (36). However, two points warrant comment. First, the mean score for the cholinergic symptom of tingling was not significantly higher during hypoglycemia than during euglycemia in either group in the present study. Thus tingling does not appear to be a very sensitive symptom of hypoglycemia. Second, although the scores were significantly higher during hypoglycemia than during euglycemia, the cholinergic symptom hungry was also prominent during euglycemia in both groups in the present study. Thus hunger does not appear to be a very specific symptom of hypoglycemia.

A limitation of the present study is the small number of adrenalectomized patients available for study. This does not compromise the fundamental conclusion that the neurogenic symptoms of hypoglycemia are largely the result of sympathetic neural, rather than adrenomedullary, activation, since that conclusion is based on a positive finding: significantly greater increments in neurogenic symptom scores during hypoglycemia compared with euglycemia in the absence, as well as in the presence, of adrenal medullae despite the small sample size. However, it does limit interpretation of the negative findings.

Compared with euglycemia, hypoglycemia caused increments in the plasma norepinephrine concentration and in the systemic norepinephrine spillover rate in subjects with intact adrenal medullae but not in those without adrenal medullae. An

Table 5. *Heart rates and systolic and diastolic blood pressures during Hypo and Eu clamps in healthy control subjects and ADX patients*

| | Time, min | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | −15 | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 |
| Nominal glucose, mg/dl | | | | | | | | | | | | |
| Hypo | | 90 | 85 | 85 | 75 | 75 | 65 | 65 | 55 | 55 | 45 | 45 |
| Eu | | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 |
| Heart rate, beats/min | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo* | 64±2 | 65±3 | 68±3 | 67±2 | 68±3 | 73±3 | 72±4 | 76±4 | 79±3 | 82±2 | 80±2 | 80±3 |
| Eu | 65±3 | 66±3 | 70±3 | 69±3 | 71±3 | 72±3 | 73±3 | 74±3 | 76±2 | 74±3 | 72±3 | 75±3 |
| ADX | | | | | | | | | | | | |
| Hypo | 62±3 | 64±4 | 69±7 | 69±7 | 70±5 | 72±4 | 72±4 | 71±3 | 71±4 | 73±5 | 72±8 | 73±7 |
| Eu | 69±4 | 75±5 | 69±3 | 77±4 | 76±4 | 76±4 | 77±4 | 76±4 | 77±4 | 78±6 | 84±5 | 80±4 |
| Systolic blood pressure, mmHg | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo | 112±3 | 113±3 | 112±3 | 113±3 | 115±3 | 114±3 | 115±3 | 112±3 | 109±4 | 110±4 | 110±4 | 111±4 |
| Eu | 113±3 | 116±3 | 116±4 | 116±4 | 117±3 | 114±4 | 115±3 | 115±4 | 115±3 | 114±3 | 115±3 | 117±4 |
| ADX | | | | | | | | | | | | |
| Hypo | 126±7 | 125±7 | 123±8 | 121±4 | 117±4 | 116±3 | 120±4 | 116±7 | 118±9 | 115±9 | 120±9 | 114±11 |
| Eu | 123±7 | 119±9 | 119±10 | 120±9 | 115±9 | 117±8 | 119±9 | 122±13 | 112±9 | 120±11 | 124±12 | 124±12 |
| Diastolic blood pressure, mmHg | | | | | | | | | | | | |
| Control | | | | | | | | | | | | |
| Hypo† | 60±2 | 62±2 | 58±2 | 59±2 | 59±2 | 58±2 | 56±2 | 56±2 | 54±3 | 51±2 | 50±2 | 50±2 |
| Eu | 62±2 | 63±2 | 60±3 | 59±3 | 60±2 | 59±2 | 58±2 | 58±2 | 58±2 | 57±2 | 59±2 | 59±2 |
| ADX | | | | | | | | | | | | |
| Hypo | 68±4 | 70±4 | 67±3 | 66±1 | 66±1 | 66±3 | 64±2 | 62±3 | 62±6 | 60±4 | 66±4 | 59±6 |
| Eu | 68±6 | 69±6 | 65±5 | 64±5 | 63±5 | 65±4 | 64±4 | 64±5 | 60±5 | 61±5 | 69±9 | 64±6 |

Values are means ± SE. *$P$ = 0.0104; †$P$ = 0.0003.

increment in the plasma norepinephrine concentration was also not observed during hypoglycemia in earlier studies of adrenalectomized patients (14, 34). With the sample size caveat just mentioned, these findings suggest that the normal plasma norepinephrine response to hypoglycemia is derived largely from the adrenal medullae. If so, whereas the plasma norepinephrine concentration is a valid index of sympathetic neural activity under basal and some stimulated conditions (1, 20, 27, 30, 34, 35), as discussed earlier, it cannot be used as an index of the sympathetic nervous system response to hypoglycemia (5, 37, 38).

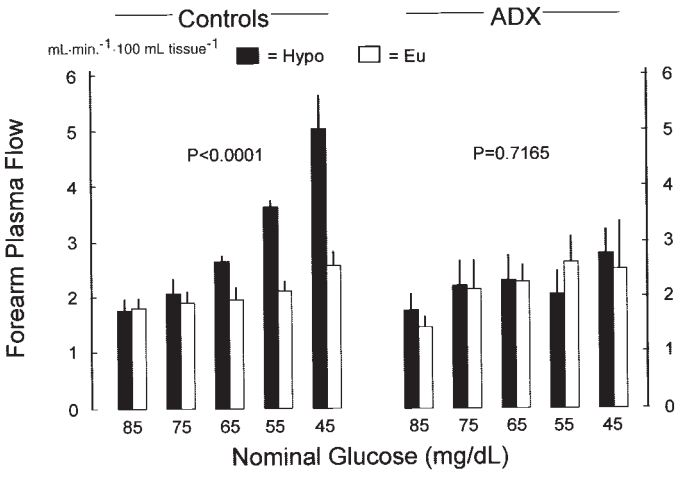


Fig. 8. Forearm plasma flow (means ± SE) over the last 10 min of each 1-h Hypo clamp step (closed bars) and at the same time points during Eu clamps (open bars) in healthy control subjects (*left*) and ADX patients (*right*).

We anticipated that hypoglycemia would increase forearm norepinephrine spillover, a measure of regional sympathetic neural activity (27, 28), in individuals with and without adrenal medullae. That was not the case. Forearm norepinephrine spillover increased during hypoglycemia in the healthy control subjects but not in the adrenalectomized patients. Although the sample size issue may well be relevant here, there was not even a trend in the direction of increased forearm norepinephrine spillover during hypoglycemia in the adrenalectomized patients. There is substantial evidence that hypoglycemia increases muscle sympathetic nerve activity measured with microneurography (8, 11, 21), and the balance of evidence indicates that it increases forearm norepinephrine spillover (Refs. 27, 28, and present data). The limitations of the forearm norepinephrine spillover method, as well as those of microneurography and tissue norepinephrine microdialysis, as a measure of regional sympathetic neural activity have been discussed in some detail (27). The forearm norepinephrine spillover method provides only an index of norepinephrine release from axon terminals of sympathetic postganglionic neurons, since the vast bulk of released norepinephrine is dissipated locally, by reuptake into the axon terminals and by local metabolism, and does not enter the circulation. It reflects norepinephrine release in only one region and therefore cannot assess regional differences in sympathetic neural activity. It involves the fundamental assumption that the tracer mixes with a constant fraction of the norepinephrine released at sympathetic nerve terminals. In addition, it is a function of forearm blood flow (which increased substantially in the healthy control subjects but not in the adrenalectomized patients in the present study). Finally, given the fact that most of the norepinephrine released from sympathetic nerves does not enter the circulation, the absence

of a measurable increase in the plasma norepinephrine concentration or the norepinephrine spillover rate does not exclude sympathetic neural activation.

Heart rate increased, diastolic blood pressure decreased, and forearm plasma flow increased during hypoglycemia, compared with euglycemia, in the subjects with, but not in those without, adrenal medullae. Again with the sample size caveat, these findings suggest that the hemodynamic responses to hypoglycemia are largely the result of adrenomedullary, rather than sympathetic neural, activation. The relevant adrenomedullary secretory product is almost assuredly epinephrine (19).

Plasma glucagon, pancreatic polypeptide, and growth hormone concentrations increased, and plasma C-peptide concentrations decreased during hypoglycemia in the absence and in the presence of adrenal medullae. These findings indicate that adrenomedullary epinephrine secretion is not critical to increased glucagon, pancreatic polypeptide, and growth hormone secretory responses and decreased insulin secretory responses to hypoglycemia. However, the blood lactate response to hypoglycemia in the healthy control subjects was not observed in the adrenalectomized patients, suggesting a role for epinephrine in that response.

Several differences between the healthy control subjects and the adrenalectomized patients are apparent. Those include the predictable virtual absence of a plasma epinephrine response to hypoglycemia in the patients. In addition, baseline plasma norepinephrine concentrations, which must have been derived from the sympathetic nervous system, appeared to be higher in the adrenalectomized patients. However, because the groups were not matched for age and gender, and the number of adrenalectomized patients studied was small, we have not provided a formal statistical contrast of the quantitative responses of the two groups.

In conclusion, these data indicate that the neurogenic symptoms of hypoglycemia are largely the result of sympathetic neural, rather than adrenomedullary, activation. They also suggest that the plasma norepinephrine and hemodynamic responses to hypoglycemia are largely the result of adrenomedullary, rather than sympathetic neural, activation.

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