Defective Epinephrine and Growth Hormone Responses in Type I Diabetes Are Stimulus Specific

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SUMMARY

The counterregulatory hormone responses to hypoglycemia and a non-glucose stimulus, exercise, were evaluated in 18 subjects with type I diabetes and in 9 normal controls. Subjects with diabetes had no overt neuropathy, with R-R variations and postural plasma norepinephrine increments that were similar to those of controls. The diabetic subjects exhibited normal increments in plasma growth hormone (GH), norepinephrine, and cortisol but blunted or absent responses in plasma epinephrine and glucagon when hypoglycemia was severe (<40 mg/dl). During a 60-min clamped reduction in plasma glucose at ~65 mg/dl, plasma GH and epinephrine increased 6- to 15-fold in controls but 2- to 4-fold in diabetics ($P < .05$). However, when subjects were exercised at this plasma glucose level (50 W for 10 min), plasma epinephrine and GH in diabetics rose markedly by 150–400% to attain the peaks reached by the controls. Plasma norepinephrine and cortisol increased to similar levels in both groups, and plasma glucagon was not significantly changed. We conclude that epinephrine and GH secretion in response to hypoglycemia are reduced in type I diabetes but that these defects are stimulus specific because the responses to exercise are not reduced. *Diabetes* 36:20–26, 1987

Counterregulatory hormones play a major role in restoring the blood glucose level to normal after hypoglycemia (1–9). In patients with type I diabetes, secretion of glucagon (3–5,10) and epinephrine (3–5,11–14) in response to hypoglycemia may be impaired. The defect in glucagon secretion appears earlier but impairment in both hormone responses is common after the first few years in patients with type I diabetes (3,4,12). Because the combined deficits in glucagon and epinephrine profoundly delay glucose recovery, such patients are at risk of more prolonged and/or severe hypoglycemia, especially when treated with intensive insulin regimens (14).

The mechanism(s) underlying these impaired counterregulatory hormone responses have not been established. Loss of afferent autonomic input (14), substrate deficiency (15), or loss of the hormone-producing endocrine tissue (16) have been postulated to be involved in the absence of appropriate counterregulatory hormone responses to hypoglycemia. However, none of these hypotheses can adequately account for the observation that counterregulatory hormone levels may be reduced in response to hypoglycemia and yet elevated inappropriately in other circumstances (3–5, 9–14,17). Thus, the defect in counterregulatory hormone secretion may, in part, be specific for the glucose signal per se.

This study was designed to compare the effects of glucose and an alternative nonglucose stimulus on the counterregulatory hormone response to hypoglycemia. To accomplish this, we employed a physiologic state—exercise—in which counterregulatory hormones are secreted in normal humans. Intensity, duration, and type of exercise all influence the extent of hormonal responses (18). In subjects with type I diabetes, the hormonal responses during exercise are complex. First, the effects of the ambient blood glucose per se may be difficult to dissociate from the influence on physical activity (19). Second, there is evidence that some of the hormonal responses to exercise are exaggerated in poorly controlled type I diabetics before the institution of glycemic control (20). We therefore utilized the glucose-clamp technique to maintain plasma glucose at desired concentrations while subjects exercised and compared the counterregulatory hormone responses during exercise at normal, elevated, or slightly reduced plasma glucose concentrations. In addition, we measured the maximal hormonal responses to more profound hypoglycemia on separate occasions in the same subjects, and patients with type I diabetes were compared with nondiabetic controls.

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MATERIALS AND METHODS

Subjects. Eighteen subjects with type I diabetes and nine normal controls were studied. The subjects with diabetes were aged 18–41 yr (29 ± 2, mean ± SE), and duration of diabetes was 3–30 yr (10 ± 2). All the subjects had a history of ketoacidosis and/or insulin treatment from the time of diagnosis. The C-peptide response to glucagon or meal challenge was absent in all but two subjects, who had low basal values that rose subnormally to 0.21 ng/ml (compared to normal responses of 9.6 ± 2 ng/ml; Human C-peptide Radioassay System, Immunex Radiochemical Diagnostics, San Diego, CA). Subjects were treated with mixtures of short- and intermediate-acting insulin in divided doses (1 subject took ultralente insulin). No other medications were taken and home blood glucose monitoring was used to achieve moderately good glycemic control. At the time of study, the total HbA_1 averaged 10 ± 0.5% (normal values, <7.5%). Three patients had HbA_1 values in the high-normal range. Evidence of clinical neuropathy was present in four subjects, three of whom had a history of hypoglycemia unawareness. Autonomic neuropathy was assessed by the variation in heart rate during deep breathing at 6 breaths/min (21) measured as the inspiratory to expiratory ratio of the R-R interval (ms) and averaged 1.27 ± 0.07 in the diabetic subjects. The maximal exercise capacity (V_{O_2max}) in these subjects was 24 ± 3 ml · min^{-1} · kg^{-1}.

The normal controls consisted of 9 nondiabetic volunteers aged 20–33 yr (25 ± 2) who had no evidence of glucose intolerance and were taking no medications at the time of study. Controls were untrained, although they had a higher V_{O_2max} (29 ± 3 ml · min^{-1} · kg^{-1}; difference not significant compared with diabetics) than the diabetics. The inspiratory: expiratory R-R ratio in controls averaged 1.48 ± 0.08 (difference not significant compared with diabetics). Both normal and diabetic groups were within 115% of ideal body weight and had no evidence of cardiovascular disease. After obtaining written informed consent, the studies were carried out in the General Clinical Research Center of the Albert Einstein College of Medicine.

Procedures. Subjects with diabetes were studied fasting in the morning after 24 h of withdrawal from intermediate- or long-acting insulin. After placement of intravenous catheters (1 in each arm), an insulin infusion (Humulin, Lilly, Indianapolis, IN) was begun (20 mU/min). Plasma glucose levels were gradually adjusted to ~100 mg/dl with the subjects supine over an average of 3 h (range, 120–480 min). After stabilization of the glucose level for at least 30 min, a priming dose of insulin (800 mU/m^2) was given in descending fashion, and plasma glucose was clamped with an exogenous infusion of 20% dextrose (22). Insulin infusion at 40 mU · m^{-2} · min^{-1} was combined with variable glucose infusion to achieve and maintain plasma glucose at the target randomly chosen for that day's experiment. The glucose targets were ~65, 100, and 200 mg/dl, designated hereafter as *low*, *normal*, and *high* glucose, respectively. The insulin infusion rate in the diabetics during high glucose was slightly greater (50 mU · m^{-2} · min^{-1}) to match the expected hyperglycemia-induced hyperinsulinemia in normal controls. Each subject was restudied on separate occasions at each target glucose at intervals ranging from 1 day to 8 wk.

After 30 min at the target glucose level, subjects were instructed to sit upright on a bicycle ergometer (Monark 868, Varberg, Sweden) for 20 min. Exercise at 50 W was initiated at 20 min and continued for 10 min. Throughout the supine, seated, and exercise periods, venous blood was sampled at 5- to 10-min intervals, and the subjects' heart rates and blood pressures were monitored.

Identical procedures were followed in normal controls, except that baseline euglycemia was sustained with a saline infusion before initiation of the clamps. The 50-W exercise represented an average work load of 57% of V_{O_2max} in the controls and 69% in diabetics (difference not significant). To assess the effect of exercise intensity on counterregulatory hormone responses, three controls were restudied with an exercise load averaging 75% of V_{O_2max} at the low and normal glucose levels.

In addition to the above experiments, the maximal counterregulatory hormone responses during severe insulin-induced hypoglycemia were evaluated. Subjects were studied after an overnight fast, and the diabetics were rendered euglycemic as above. With the subjects supine, an insulin infusion (40 mU · m^{-2} · min^{-1}) was initiated and continued for 60 min. By 30 min, plasma glucose had declined below 40 mg/dl, and all subjects had become symptomatic of hypoglycemia. Blood was withdrawn at 5- to 15-min intervals for determination of plasma glucose and counterregulatory hormone concentrations.

Measurements. Plasma glucose was determined with a Beckman glucose analyzer (Beckman, Fullerton, CA). Plasma free insulin was determined in diabetics after precipitation of plasma at 37°C with ice-cold polyethylene glycol (PEG 6000, 25%, Eastman Kodak, Rochester, NY). The remainder of the sample was centrifuged at 4°C, and the plasma was separated and frozen at −20°C for subsequent analysis. Plasma insulin was determined with a double-antibody assay (23). Plasma glucagon was measured with Unger antibody 30K (24). Plasma cortisol (25) and GH (26) were determined by radioimmunoassay, and plasma epinephrine and norepinephrine were determined by an isotope-derivative method (27).

Statistical analyses were performed with an analysis of variance and paired and unpaired Student's *t* tests where appropriate (28).

RESULTS

Counterregulatory hormone response to severe hypoglycemia. We first sought to establish the counterregulatory hormone response to a maximal hypoglycemic stimulus. In the nondiabetic controls, fasting plasma glucose averaged 102 ± 2 mg/dl, which was not significantly different from that in diabetics (98 ± 5 mg/dl) after basal insulin infusion (Fig. 1). The infusion of insulin at 40 mU · m^{-2} · min^{-1} resulted in a plasma glucose nadir value (37 mg/dl), which was identical to that in controls at 30 min. Before termination of the insulin infusion at 60 min, plasma glucose had begun to return spontaneously to baseline in controls. In the diabetics, plasma glucose remained <50 mg/dl until 90 min; one of the diabetic subjects required glucose infusion because of a persistent decline in plasma glucose to <30 mg/dl. Plasma free insulin (not shown) reached values similar to those in controls (~60 μU/ml) by 60 min, before returning to basal concentrations (~15 μU/ml) by 90 min.

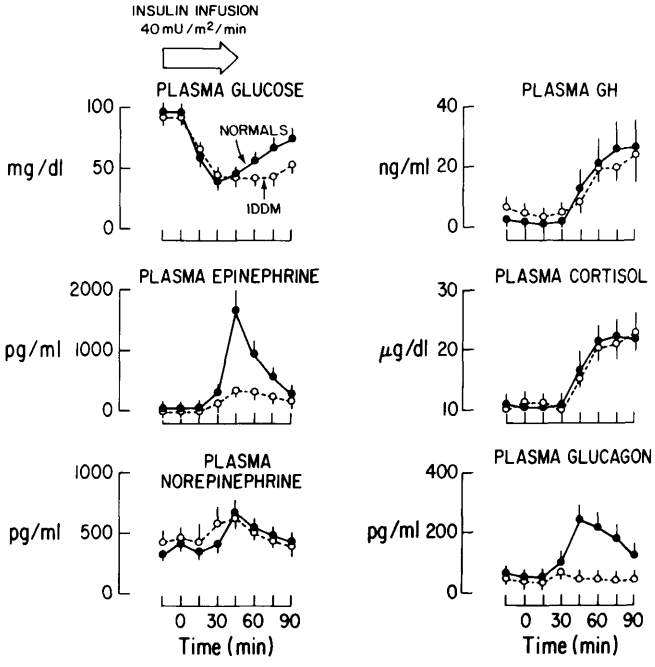

FIG. 1. Effect of hypoglycemia induced by insulin infusion on plasma glucose and counterregulatory hormones in controls and diabetics.

Basal values of the counterregulatory hormones (Fig. 1) were similar in the two groups, although plasma GH concentrations were somewhat elevated in the diabetics ($.10 > P > .05$). Despite the similar (and actually more prolonged) hypoglycemic stimulus in the diabetics, plasma epinephrine and glucagon concentrations failed to achieve the values attained by controls (Fig. 1). Peak plasma epinephrine and glucagon were each only 27% of the corresponding values in controls ($P < .005$). The impairment in epinephrine and glucagon responses was, however, not true for the remaining counterregulatory hormones. Identical peak values of norepinephrine, cortisol, and GH were seen with hypoglycemia. In particular, individual subjects displayed GH levels that peaked at 27 ± 10 ng/ml in controls and 32 ± 14 ng/ml in diabetics (difference not significant), and all diabetics and controls had peak GH values >10 ng/ml.

Glucose-clamp studies. Table 1 details the plasma norepinephrine and cardiovascular responses in both groups at the three different glucose clamp levels. At all glucose levels with the subjects supine, heart rate in diabetics was greater than in controls ($P < .05$). With assumption of the seated-upright position, there were no significant changes in heart rate or blood pressure in either group; however, after exercise, heart rate increased significantly and proportionately by ~65%. Plasma norepinephrine increased when the subjects were seated; further increases during exercise were comparable in both groups, except for a greater plasma norepinephrine response in diabetics during exercise at low glucose (Table 1).

Figure 2 shows plasma glucose concentrations achieved and maintained during the final 60 min of the glucose-clamp studies. To ensure stability of the plasma glucose level, we calculated the coefficient of variation (C.V.) for each of the two groups at each of the three plasma glucose target levels. In normal subjects, C.V.s averaged 9.3, 6.9, and 10.8% for low-, normal-, and high-glucose clamps, respectively. In diabetics, the corresponding C.V.s were 10.5, 8.5, and 6.8% and did not differ significantly from those of controls. Plasma glucose during the normal-glucose clamps averaged 95 ± 4 mg/dl before exercise and 101 ± 7 mg/dl after exercise in nondiabetic controls (difference not significant). For diabetics, the corresponding plasma glucose levels were 104 ± 2 and 108 ± 5 mg/dl, respectively (difference not significant). There were no differences between the plasma glucose levels when comparing controls and subjects with type I diabetes. Similarly, at low glucose (~65 mg/dl) and high glucose (~195 mg/dl), controls and diabetics did not differ in plasma glucose concentration, and the changes in pre- and postexercise plasma glucose were not significant (Fig. 2).

Plasma free-insulin concentrations in the three glucose-clamp studies were similar. The average plasma insulin levels over the 60-min study were 78 ± 12, 78 ± 12, and 87 ± 12 μU/ml in controls during low, normal, and high glucose,

TABLE 1
Blood pressure, pulse, and plasma norepinephrine responses to upright position and exercise in diabetics and controls

	Low glucose			Normal glucose			High glucose		
	Supine	Upright	Exercise	Supine	Upright	Exercise	Supine	Upright	Exercise
Diabetics									
Blood pressure (mean arterial, mmHg)	91 ± 3	87 ± 4	96 ± 4	92 ± 2	92 ± 3	98 ± 3	98 ± 3	93 ± 4	97 ± 3
Pulse (beats/min)	72 ± 4*	75 ± 8*	126 ± 7*	74 ± 3*	78 ± 9*	125 ± 6*	78 ± 2*	76 ± 5*	141 ± 11*
Plasma norepinephrine (pg/ml)	524 ± 126	746 ± 147	1206 ± 156*	399 ± 75	630 ± 117	965 ± 148	385 ± 109	619 ± 170	948 ± 204
Controls									
Blood pressure (mean arterial, mmHg)	93 ± 4	92 ± 5	88 ± 4	87 ± 3	90 ± 3	92 ± 5	88 ± 6	88 ± 3	93 ± 4
Pulse (beats/min)	65 ± 5	68 ± 7	105 ± 9	65 ± 6	65 ± 6	118 ± 8	64 ± 4	71 ± 3	121 ± 9
Plasma norepinephrine (pg/ml)	373 ± 25	565 ± 77	765 ± 106	398 ± 74	637 ± 89	850 ± 126	419 ± 23	723 ± 106	1119 ± 329

Data are presented as means ± SE.
*$P < .05$ compared with equivalent value in controls.

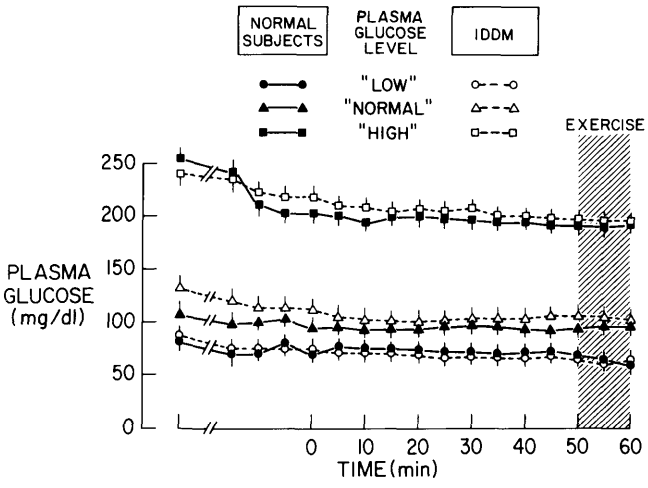

Fig. 2. Plasma glucose concentrations during final 60 min of each glucose clamp as low, normal, and high glucose in controls and diabetics. Ten-minute exercise period is shown in *shaded area*.

respectively, and 77 ± 11, 79 ± 7, and 81 ± 11 μU/ml in diabetics.

Counterregulatory hormone responses in low-glucose studies. The plasma epinephrine responses to low glucose are depicted in Fig. 3. Before perturbation of plasma glucose, basal plasma epinephrine values were identical in the two groups. With reduction to low glucose and before exercise, however, plasma epinephrine rose six- to sevenfold in controls but only two- to threefold in diabetics ($P < .001$). After 10 min of exercise, plasma epinephrine rose only slightly (9%) in controls but 150% in diabetics ($P < .005$). This increase in plasma epinephrine was sufficient to raise hormone levels in diabetics to concentrations not significantly different from controls (Fig. 3). In normal controls reexercised at 75% V_{O_2max}, plasma epinephrine increased to 233 ± 30 pg/ml, levels comparable to those during the lesser exercise intensity of 50 W and not significantly different from the effect of 50-W exercise in diabetics.

Similar results were observed for GH. As seen in Fig. 3, basal GH levels were comparable in the two groups but rose to 14 ± 4 ng/ml in controls and to only 4 ± 1 ng/ml in diabetics during low glucose ($P < .05$). Exercise potentiated the GH response fourfold in diabetics such that plasma GH rose to 17 ± 6 ng/ml in diabetics but only by 40% in controls ($P < .05$). Again, when the effect of more intense exercise of the same duration was evaluated in controls (75% V_{O_2max}), the GH increment to 12 ± 4 ng/ml was not significantly different from the exercise at 50 W for both groups shown in Fig. 3.

In contrast to the exercise-induced augmentation of plasma epinephrine and GH responses to low glucose in diabetics, the blunted plasma glucagon rise during low glucose remained unchanged. Basal plasma glucagon (when diabetic subjects were euglycemic during insulin infusion) was 54 ± 18 pg/ml, which was lower than the corresponding basal value in controls (131 ± 37 pg/ml; $P < .05$). However, this discrepancy may have been due to elevated basal glucagon concentrations in one of the normal subjects. If this subject's data are excluded, basal glucagon levels in controls were 96 ± 28 pg/ml (difference not significant). Plasma glucagon tended to rise during low glucose alone (112 ± 21 pg/ml in controls and 62 ± 11 pg/ml in diabetics) and when combined with 50-W exercise (142 ± 31 in controls and 81 ± 9 pg/ml in diabetics), but the increments were not significant. For plasma cortisol, basal values in controls and diabetics (11 ± 3 and 8.5 ± 1 μg/dl, respectively) were comparable and increased gradually with hypoglycemia; the difference from baseline, however, was only significant by the end of the exercise period (to 17 ± 2 in controls and 14 ± 2 μg/dl in diabetics; both $P < .05$ compared with baseline).

Counterregulatory hormone responses in normal- and high-glucose clamps. The plasma levels of epinephrine and GH observed during the clamps at normal (~95 mg/dl) and high (~195 mg/dl) glucose are summarized in Fig. 4. Before exercise at both normal and high glucose, plasma GH levels in diabetics were about twofold greater than in controls ($P < .01$–$.05$), whereas the preexercise plasma epinephrine values were similar in the two groups and at the two glucose levels. Exercise in the subjects with type I diabetes produced a 48% increase in plasma GH at normal glucose and a 70% increase at high glucose ($P < .01$ for each); no increase in plasma GH was noted in controls. For plasma epinephrine, however, both normal controls and diabetics displayed significant increments with exercise. In normals, plasma epinephrine increased by 20–50% with exercise ($P < .01$), although the increase at both normal and high glucose was less than the significantly greater 90–120% increments displayed by diabetics (Fig. 4). In exercise studies at 75% V_{O_2max} in normal controls, plasma epinephrine and GH increases were similar to those during normal glucose at 50 W (not shown). Plasma cortisol and glucagon were unaf-

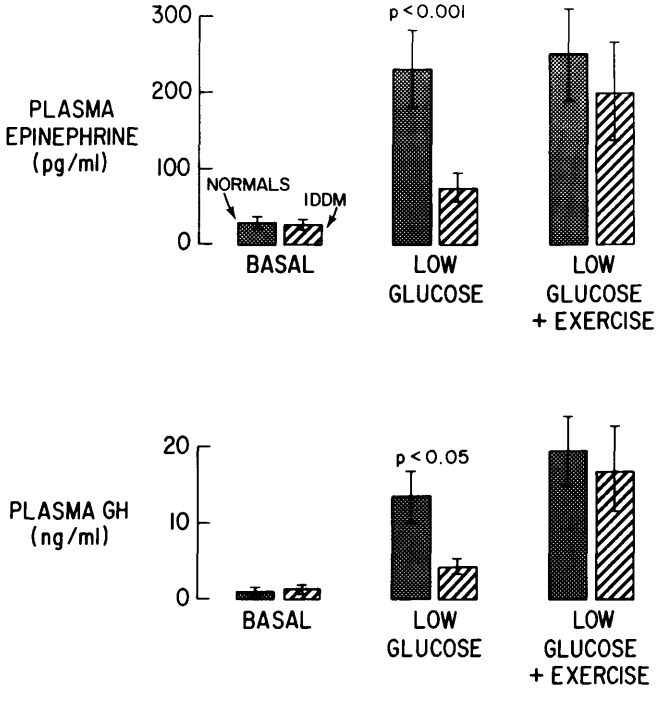

FIG. 3. Plasma epinephrine and GH responses in low glucose clamp studies. Mean values are shown for both groups of subjects before induction of low glucose [basal], before exercise, and after 10-min of low glucose together with exercise.

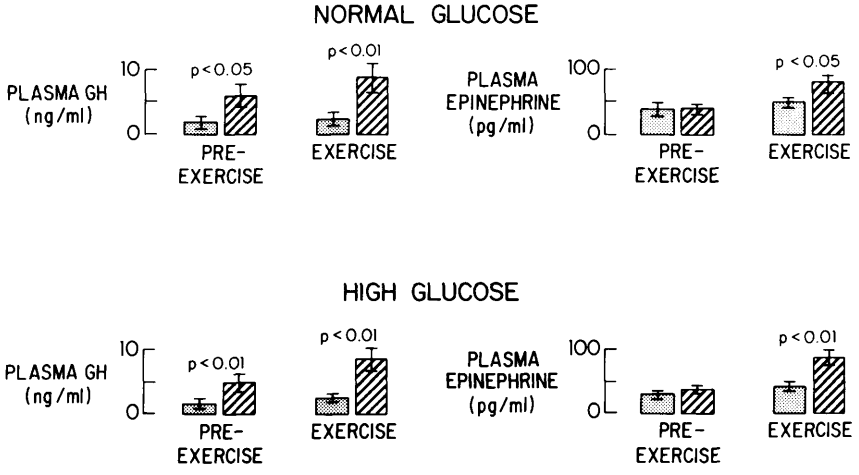

FIG 4. Results of plasma GH and epinephrine responses during normal- and high-glucose clamps in diabetics (*hatched bars*) and controls (*shaded bars*).

fected by glucose manipulations or exercise during normal and high glucose (not shown). Plasma norepinephrine changes (Table 1) paralleled the increments with position and exercise seen at low glucose; both controls and diabetics exhibited similar responses.

DISCUSSION

There is an accumulating body of evidence indicating that impaired counterregulatory hormone responses to hypoglycemia may be observed in subjects with type I diabetes (3–5,10–14), apparently independent of the phenomenon seen in patients with overt and severe autonomic neuropathy secondary to long-standing diabetes (16,29). Gerich and coworkers (10) first demonstrated that blunted glucagon responses to hypoglycemia were present in patients with type I diabetes but not in type II, implying a specific α-cell defect. This observation has been explored by others (30,31), and the evidence suggests that this defect is temporally related to the duration of type I diabetes (3), may also occur in type II diabetes (32), and remains despite normalization of glycemia (33–34). Subsequent reports have described defects in epinephrine responses to hypoglycemia in type I diabetes (3–5,11–14). It has thus been emphasized that the two counterregulatory hormones responsible for rapid restoration of blood glucose after hypoglycemia may be reduced in the group of patients most vulnerable to hypoglycemia (11,14). Our current data on the counterregulatory hormone responses to severe hypoglycemia are consistent with these observations: all of our patients exhibited a blunting or absence of plasma epinephrine and glucagon levels during insulin-induced hypoglycemia.

To assess the specificity of the impaired counterregulatory hormone responses, the same subjects were evaluated during a period of clamped glycemia and submaximal cycle exercise. Thus, we were able to compare the counterregulatory hormone response to exercise at various plasma glucose levels. With moderate hypoglycemia (plasma glucose, ~65 mg/dl) sustained over the course of a 60-min glucose clamp, the defective responses for plasma epinephrine and glucagon seen with severe hypoglycemia persisted. In addition, the GH response was also found to be reduced in diabetics. However, when diabetics were exercised at 50 W for 10 min, both plasma epinephrine and GH rose to levels comparable with values achieved in controls without further decrements in plasma glucose. These studies clearly suggest that epinephrine and GH responses are impaired during moderate hypoglycemia in type I diabetes but that these defects are partly related to the nature of the stimulus and not due to absolute failure of hormone secretion.

The importance of the glucagon secretory defect during hypoglycemia relates partly to the role it plays in the acute counterregulatory cascade (1,2). A paradoxical observation is that, although deficient during hypoglycemia, glucagon secretion in response to other stimuli may be normal or exaggerated (14); for example, striking elevations may occur in diabetic ketoacidosis (17). Our subjects' responses to hypoglycemia confirm the data in the literature: neither an acute fall in plasma glucose to <40 mg/dl nor sustained maintenance of modest hypoglycemia (~65 mg/dl) resulted in appreciable increases in plasma glucagon in the type I diabetics. In addition, we did not observe exercise-induced increments in plasma glucagon in either controls or diabetics. This might be attributable to the duration and/or magnitude of our exercise stimulus because more severe exercise may be necessary to elicit plasma glucagon responses in normal humans (18).

The concomitant presence of an epinephrine secretory defect in type I diabetics has been amply documented in the literature (3–5,11–14). We found a marked attenuation of the plasma epinephrine rise during severe hypoglycemia in our patients that was similar to that reported in other studies (3,4,12,14). In addition, when we clamped plasma glucose at ~65 mg/dl, reduced plasma epinephrine responses were also seen in the diabetics. Thus, reduction in plasma glucose to the low-normal range of glycemia capable of triggering counterregulatory hormones resulted in a reduced epinephrine increment in diabetics. Figure 5 depicts the relationship between the logarithm of plasma epinephrine level and the average plasma glucose concentration across the ranges studied. The displacement of the curve toward the left in the diabetics suggests that the glucose threshold for epinephrine secretion is reduced in subjects with type I dibetetes.

In contrast to the impaired glucagon and epinephrine responses during both severe hypoglycemia and sustained low-glucose clamp, GH secretion was notably divergent in

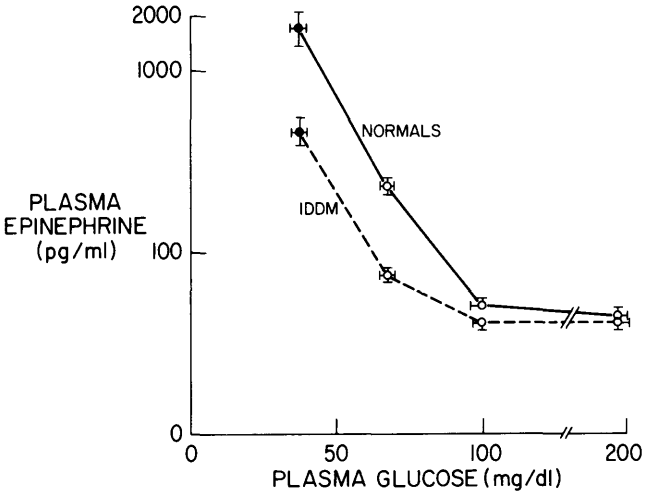

FIG. 5. Relation between logarithm of mean plasma epinephrine values and ambient plasma glucose concentration. ○, Clamped glucose level; ●, during severe hypoglycemia.

the diabetics in the two different studies. Controls exhibited the expected 10-fold GH response to low glucose. In marked contrast, diabetics displayed a minimal rise in GH during the 50-min low-glucose clamp, although they had responses identical to those of controls during the maximal hypoglycemic stimulus. Deficient GH responses to hypoglycemia have been reported to occur in type I diabetes (13,14). Our ability to demonstrate this defect only during low-glucose clamps suggests that the release of GH in controls is exquisitely sensitive to glycemic changes in the range between 65 and 100 mg/dl and that there is loss of this sensitivity in insulin-infused type I diabetics. However, with more profound and acute hypoglycemia, GH responses are maximal and comparable with those of controls (Fig. 6). This alteration in GH responsiveness to hypoglycemia in type I diabetes is shown in Fig. 6 as a displacement to the left of the relationship between the plasma glucose level and the logarithm of the GH concentration. As for plasma epinephrine responsiveness to reductions in plasma glucose, these data suggest that alteration of the threshold for GH secretion occurs in type I diabetes. Note, however, that the rapidly achieved severe hypoglycemia and the low glucose studies represent two different models of hypoglycemia, which may explain the divergence of the GH responses in type I diabetes.

One suggested mechanism underlying these defective counterregulatory hormone responses is the presence of neuropathy. In our subjects, *1*) clinically evident peripheral neuropathy was only present in four diabetics, *2*) the changes in blood pressure and plasma norepinephrine after assumption of upright posture were normal, and *3*) the expiratory-to-inspiratory ratio of R-R variation was not significantly reduced. Although baseline heart rate was higher in diabetics than in controls, indicating possible vagal neuropathy, heart rate increments varied normally with change in position or with exercise. Nevertheless, the existence of autonomic neuropathy in diabetes and its potential effect on counterregulatory hormone secretion may be difficult to assess (35). Defective epinephrine secretion in diabetics is probably due to a spectrum of causes, with the most severe defects being due to autonomic neuropathy at one extreme.

Recent studies in type I diabetics suggest that intensive insulin treatment produces a further decline in the counterregulatory hormone responses to hypoglycemia (36). Note that our studies were not conducted in intensively treated subjects and that mean HbA_1 values were not normal. Also, other studies have not found further reductions of counterregulatory responses to hypoglycemia in intensively treated patients (34). Nevertheless, intermittent hypoglycemia even during conventional therapy may have occurred in our subjects and contributed to the decreased counterregulatory hormone responsiveness during experimental hypoglycemia. Interestingly, a proposed mechanism for alterations in neural function mediated by chronic hyperglycemia in the rat is related to changes in glucose transport across the blood-brain barrier (37), suggesting that there may indeed be adaptation to glycemia.

The similarity between the defective responses in plasma epinephrine and GH with low glucose but with restoration of these counterregulatory hormone levels with exercise was remarkable. However, different mechanisms may have accounted for these apparent similarities. Because previous studies have suggested that conventionally treated diabetics have exaggerated counterregulatory hormone responses to exercise (which were reversed by 2 wk of insulin-infusion pump therapy) (38), our results may represent the superimposition of a defective response to low glucose on an abnormal response to exercise with a consequent "averaging" of the increments in plasma epinephrine and GH. Indeed, this notion is supported by our results in the normal- and high-glucose clamps (Fig. 4), wherein greater increments in both counterregulatory hormones were seen during exercise in diabetics but not in controls. In contrast to the previous studies (38), however, we did not see exaggerated plasma norepinephrine responses to exercise in diabetics. Also, the magnitude of the plasma epinephrine and GH hyperresponsiveness in the diabetics during exercise at normal or high glucose was smaller than the exercise-induced increases in these counterregulatory hormones at low glucose. Taken together, these data clearly indicate that submaximal exercise potentiates the deficient plasma epinephrine and

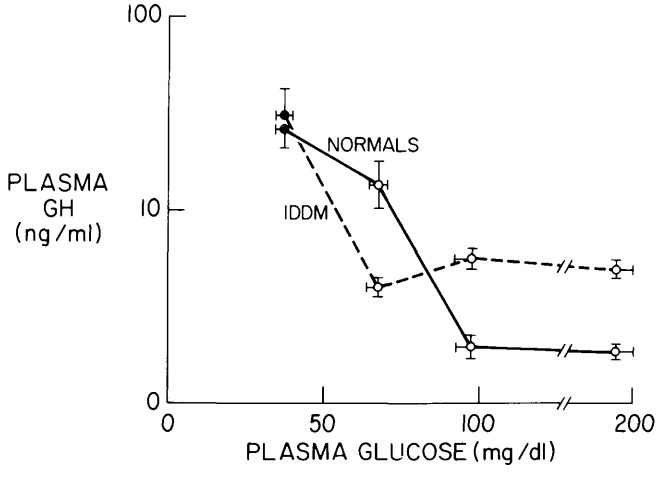

FIG. 6. Relationship between logarithm of mean plasma growth hormone and ambient glycemia. ○, Clamped glucose levels; ●, during severe hypoglycemia.

GH secretion induced by modest hypoglycemia in type I diabetes.

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