Pituitary Response to Growth Hormone–releasing Factor in Diabetes

Failure of Glucose-mediated Suppression

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SUMMARY

To evaluate the mechanism underlying raised growth hormone levels in diabetes, we compared the response to growth hormone–releasing factor (GRF) in type I diabetic and healthy control subjects. In 12 poorly controlled diabetic subjects (fasting plasma glucose 276 ± 27 mg/dl) basal serum growth hormone levels were elevated by 200–300% ($P < 0.02$), yet the incremental increase in growth hormone after GRF injection was no greater than in control subjects. Furthermore, five additional diabetic subjects with normal growth hormone levels after long-term insulin pump treatment also showed an identical response to GRF. Thus, raised basal growth hormone levels in diabetes and the fall that follows intensive insulin treatment may reflect changes in hypothalamic regulation of, rather than in pituitary responsiveness to, GRF. However, when five normal subjects were restudied during glucose infusion, even quite modest hyperglycemia (plasma glucose ~150 mg/dl) caused marked suppression of the response to GRF ($P < 0.005$). Thus, the "normal" response to GRF in poorly controlled diabetes is actually inappropriate. Failure of the pituitary to suppress in response to hyperglycemia in diabetes implies a second abnormality that may further aggravate disordered growth hormone secretion. DIABETES *33*:804–806, August 1984.

Raised growth hormone levels in diabetes have recently been shown to intensify and perpetuate the metabolic abnormalities associated with poor control.[1] Furthermore, it has been suggested that growth hormone may play an important role in the development of diabetic retinopathy.[2] Growth hormone levels are commonly increased in poorly controlled diabetes and return to normal after intensive insulin treatment.[3–5] The disturbance in growth hormone secretion is characterized not only by elevated basal concentrations, but also by exaggerated responses to provocative stimuli[5,6] and a failure to suppress normally with glucose.[6–8]

The present study was undertaken to examine the extent to which this disordered regulation of growth hormone secretion reflects alterations in pituitary sensitivity to growth hormone–releasing factor (GRF). To take account of any effect of hyperglycemia on pituitary response in the diabetic subjects, we also administered GRF during glucose infusion in control subjects.

METHODS

Subjects. Seventeen randomly selected nonobese type I diabetic individuals, aged 18–42 yr (duration of diabetes 9–30 yr), were studied. In none was there a detectable C-peptide response to intravenous glucagon. Apart from diabetes, patients were in good health and none was taking medications other than insulin. Twelve (three men, nine women) were treated conventionally with one or two injections of insulin daily (total daily dose, 29–75 U/day). The other five (two men, three women) had been treated intensively with the insulin pump as previously described[9] for 2–48 mo before study (insulin dose, 32–65 U/day). Eight healthy subjects (six men, two women) aged 26–36 yr acted as controls. All subjects gave written consent to the study, which was approved by the Human Investigations Committee of Yale University School of Medicine.

Procedures. All studies were performed after an overnight fast. An indwelling catheter was inserted into an antecubital vein for blood sampling and for GRF administration. Subjects then rested in the recumbent position for at least 2 h before GRF was given. Human pancreatic tumor GRF (hpGRF-40 OH), synthesized as previously described,[10] was given as a bolus of 0.3 μg/kg.

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TABLE 1
Fasting plasma glucose, glycosylated hemoglobin, basal serum growth hormone, and peak serum growth hormone after GRF bolus in controls, conventionally treated diabetic patients, and diabetic patients treated intensively with the insulin pump

	Control subjects (N = 8)	Diabetic subjects	
		Conventional (N = 12)	Insulin pump (N = 5)
Glucose (mg/dl)	85 ± 3	276 ± 15*	118 ± 15
Hemoglobin A1 (%)	5.9 ± 0.2	12.5 ± 0.9*	7.9 ± 0.4*
Basal GH (ng/ml)	2.1 ± 0.5	7.1 ± 1.8†	2.8 ± 1.6
Peak GH (ng/ml)	30 ± 3	30 ± 5	27 ± 7

Significance of difference from controls: *$P < 0.001$; †$P < 0.02$.

Two groups of studies were performed. In the first, the response to GRF in both conventionally and pump-treated diabetic subjects was compared with that of control subjects. Conventionally treated diabetic patients received no insulin on the morning of study, while pump-treated patients remained on their basal insulin infusion rate throughout. In the second group of studies, the effect of glucose on the response to GRF in five normal subjects was examined. Each subject received either glucose or saline through a second catheter on two separate occasions in random order. When glucose was administered, plasma glucose was raised to ~150 mg/dl 2 h before giving GRF, and was maintained at this level thereafter by a variable glucose infusion (glucose clamp technique).[11]

Analyses. Plasma glucose was measured on a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, California). Plasma insulin and serum growth hormone (using a National Institutes of Health standard) were measured by radioimmunoassay as previously described.[12] Total glycosylated hemoglobin was determined using a mini-column procedure (Isolab Inc., Akron, Ohio).

Data are presented as mean ± SEM. Paired and unpaired Student's *t* tests were used for statistical analyses.

RESULTS

In conventionally treated diabetic subjects, elevated levels of plasma glucose and glycosylated hemoglobin were accompanied by a 3–4-fold increase in basal growth hormone concentrations (Table 1). However, as shown in Figure 1, the rise in growth hormone levels after GRF was no greater than in normal control subjects. Diabetic patients treated with the insulin pump had near-normal values of glucose and glycosylated hemoglobin (Table 1). In these patients, basal serum growth hormone levels were indistinguishable from those of normal control subjects, yet the response to GRF was the same as in the conventionally treated diabetic patients (Table 1).

When glucose was infused into control subjects, plasma glucose was acutely raised to ~150 mg/dl and remained at 148 ± 7 mg/dl throughout the study. Plasma insulin averaged 59 ± 5 μU/ml during the 3 h after GRF. This compared with insulin levels of 10 ± 1 μU/ml on the control day when the plasma glucose was 85 ± 2 mg/dl. Figure 2 shows the effect of this hyperglycemia on the response to GRF. Glucose infusion suppressed the peak increase in growth hormone levels by 65% (from 25 ± 4 to 9 ± 2 ng/ml, $P < 0.005$).

DISCUSSION

The association between poorly controlled diabetes and elevated growth hormone levels is well recognized.[1,3,4] Initially, interest focused on growth hormone's possible role in mediating diabetic microvascular complications.[2] More recently it has been shown to play an active role in perpetuating the metabolic abnormalities of diabetes.[1]

Although growth hormone levels are often high in diabetes, levels of insulin-like growth factor I (IGF I, somatomedin-C), which is normally stimulated by growth hormone, are normal or low.[13] Improved metabolic control with the insulin pump results in a rise in IGF I despite a fall in serum growth hormone levels,[13] suggesting that poor diabetes control causes

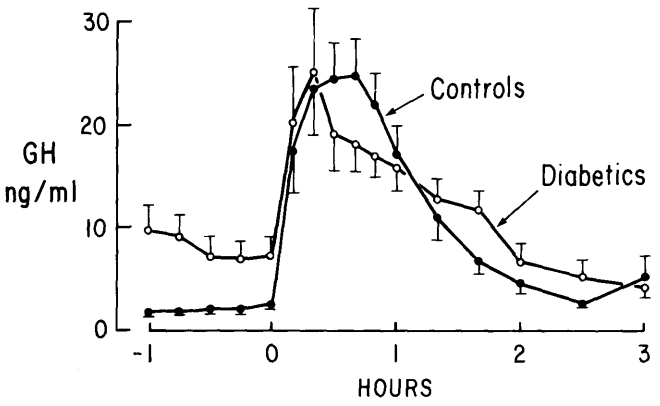

FIGURE 1. Growth hormone response to hpGRF-40 (0.3 μg/kg i.v.) in conventionally treated type I diabetic and healthy control subjects.

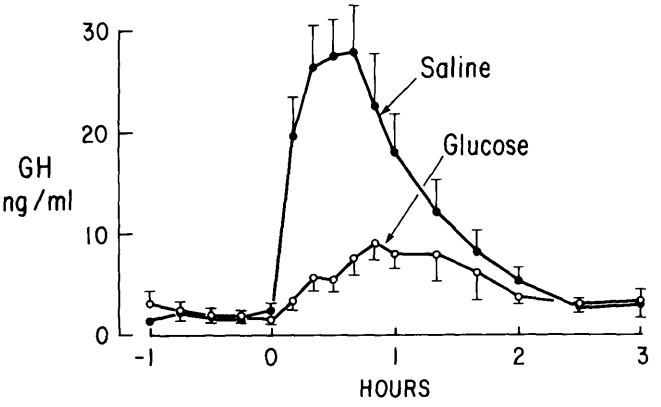

FIGURE 2. Growth hormone response to GRF in control subjects when infused with either glucose or saline.

a reversible defect in the generation of IGF I. Raised growth hormone levels in diabetes may thus be a normal homeostatic response, whereby the pituitary attempts to maintain normal levels of IGF I.

Growth hormone secretion is regulated by two hypothalamic peptides, growth hormone–releasing factor (GRF) and somatostatin, which stimulate and inhibit growth hormone secretion, respectively.[14] There is, as yet, no evidence that IGF I regulates growth hormone secretion via GRF. Rather, studies in the rat suggest that feedback control of growth hormone secretion by IGF I is exerted both directly on the pituitary and indirectly by stimulation of hypothalamic somatostatin.[15] If the same is true in man, one might anticipate an exaggerated response to GRF in poorly controlled diabetes. We therefore gave diabetic subjects synthetic hpGRF-40 (which is probably identical to a hypothalamic GRF[16]) to directly test this possibility.

Despite high basal growth hormone levels, the peak growth hormone level in poorly controlled diabetic patients given exogenous GRF was no different from controls. Indeed the incremental increase in growth hormone tended if anything to be reduced. Furthermore, in pump-treated diabetic patients whose basal growth hormone levels were normal, the response to GRF was no different from poorly controlled patients. These data imply that changes in basal growth hormone levels in diabetes may result from changes in hypothalamic regulation of, rather than in pituitary responsiveness to, GRF. If this reflects altered feedback by IGF I, the feedback is probably exerted primarily at hypothalamic rather than at pituitary level.

Glucose is well known to inhibit growth hormone secretion in normal subjects.[6,8] Therefore, to take account of any effect of glucose on the pituitary and to assess the appropriateness of the diabetic patients' response to GRF in the context of their hyperglycemia, we also gave GRF to normal subjects made hyperglycemic with intravenous glucose. Although the resultant plasma glucose levels were considerably lower than those of the diabetic subjects, the growth hormone response to GRF was markedly suppressed. Thus, while the pituitary response in poorly controlled diabetic patients was normal in absolute terms, it was nevertheless quite inappropriate for the prevailing plasma glucose levels. This failure of the pituitary to suppress in response to hyperglycemia implies a second abnormality that would tend to further aggravate the disordered growth hormone secretion.

Although pituitary suppression by glucose could be due to a direct effect, it is probably more likely that glucose acts indirectly by stimulating hypothalamic somatostatin secretion. This possibility is consistent with evidence that glucose stimulates somatostatin secretion from pancreatic islets in animals[17] and increases circulating somatostatin levels in normal man.[18] It is tempting to speculate that impaired growth hormone suppression by glucose in diabetes could reflect defective regulation of hypothalamic somatostatin secretion and that this could represent a more generalized defect, contributing to the analogous disturbances in glucagon secretion seen in poorly controlled type I diabetes.[19]

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