No Evidence For Increased Growth Hormone Responses to Growth Hormone–Releasing Hormone in Patients With Diabetic Retinopathy

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SUMMARY

Several studies report increased growth hormone (GH) responses to provocative stimuli in patients with diabetic retinopathy. We studied GH responses to 1 μg/kg body wt human pancreatic GH-releasing hormone 1–44 (hpGHRH 1–44) in 33 patients with type I diabetes mellitus, 31 patients with type II diabetes mellitus, and 2 control groups (*N* = 11 and 8). Based on the results of fundoscopy and fluorescein angiography, the diabetic patients were subdivided into *1*) patients without diabetic retinopathy, *2*) patients with nonproliferative diabetic retinopathy, and *3*) patients with proliferative diabetic retinopathy. Growth hormone responses to hpGHRH 1–44 in diabetic patients with proliferative or nonproliferative retinopathy or without retinopathy were not significantly different regardless of the type of diabetes. Remarkably, GH responses to hpGHRH 1–44 in type I diabetic patients without retinopathy were significantly higher than the matched controls. Our data suggest that diabetic retinopathy in type I and in type II diabetes is not associated with increased GH responsiveness to hpGHRH 1–44, whereas in type I diabetes mellitus without diabetic retinopathy, a GH hyperresponsiveness to hpGHRH seems to occur. *Diabetes* 36:159–62, 1987

Despite intensive investigation, the causes of diabetic retinopathy (DRP) have not been clearly determined. Increasing evidence suggests that multiple factors are involved (1). Among them, growth hormone (GH) has been suggested as a causative factor in the development of DRP (2). In the literature, various abnormalities of GH secretion, e.g., hyperresponsiveness to provocative stimuli (3), have been observed in diabetes mellitus. Several authors studied GH responsiveness in patients with DRP; unspecific stimuli for GH secretion were used, and the results conflict (4–6).

Recently, Kaneko et al. (7) reported an increased GH response to human pancreatic GH-releasing hormone (hpGHRH) in 10 patients with DRP compared with 7 patients without DRP. Taking into account age, duration of diabetes, and treatment of Kaneko's patients, we conclude that the authors primarily investigated type II diabetic patients.

To the best of our knowledge, GH responses to hpGHRH in type I diabetic patients with DRP have not been studied. In this context, the type of diabetes seems to be of particular interest because a recent study reported different GH responses to hpGHRH in the two types (8). To support the hypothesis of GH hyperresponsiveness in patients with DRP, we investigated GH responses to hpGHRH in diabetic patients and control subjects, taking into account the type of diabetes and various degrees of DRP as well.

PATIENTS AND METHODS

We studied 33 patients with type I diabetes mellitus and 30 patients with type II diabetes mellitus according to the classification of the National Diabetes Data Group (9); 16 normal subjects matched for type I diabetic patients and 8 normal subjects matched for type II diabetic patients served as controls. All subjects gave their informed consent. The diabetic patients were subdivided according to the results of fundoscopy and fluorescein angiography into three groups as defined by Palmberg (10): patients without DRP, patients with nonproliferative DRP (NPDRP), and patients with proliferative DRP (PDRP). Clinical characteristics of diabetic patients and controls are shown in Table 1. Age and body mass index in type I and type II diabetic patients were not significantly different from corresponding control subjects. Age, body mass index, HbA_{1c}, and fasting plasma glucose levels in the three groups of type I diabetic patients and type II diabetic patients did not differ significantly.

After an overnight fast, the subjects were recumbent for at least 2 h, and then an intravenous catheter was placed

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TABLE 1
Clinical characteristics of type I and type II diabetic patients subdivided into groups of patients without diabetic retinopathy (DRP), with nonproliferative diabetic retinopathy (NPDRP), and with proliferative diabetic retinopathy (PDRP) and controls

Patients	N	Age (yr)	Body mass index (kg/m²)	Diabetes duration (yr)	HbA_{1c}* (%)	Fasting plasma glucose (mg/dl)
Type I						
Without DRP	12	30.2 ± 4.0	22.6 ± 1.3	6.9 ± 2.7	8.4 ± 0.4	161 ± 20
With NPDRP	11	36.8 ± 4.2	24.2 ± 1.0	20.2 ± 1.5	8.1 ± 0.5	197 ± 33
With PDRP	10	34.3 ± 3.6	24.5 ± 0.9	22.7 ± 2.9	8.6 ± 0.5	231 ± 31
Controls	11	29.6 ± 1.5	21.5 ± 0.9		4.7 ± 0.2	78 ± 3
Type II						
Without DRP	16	60.6 ± 2.8	27.3 ± 1.5	9.2 ± 1.6	8.4 ± 0.4	147 ± 11
With NPDRP	8	57.8 ± 2.0	27.1 ± 0.9	11.3 ± 1.9	8.4 ± 0.6	133 ± 20
With PDRP	6	68.7 ± 2.6	28.0 ± 1.4	19.8 ± 2.1	8.2 ± 0.6	121 ± 34
Controls	8	55.3 ± 5.9	27.0 ± 1.4		5.1 ± 0.2	79 ± 4

*Normal range <6.0%.

in a suitable antecubital vein. No medication was given on the morning of the test. Blood samples were obtained before (−30 and 0 min) and after (15, 30, 45, 60, and 90 min) a bolus injection of 1 μg/kg body wt i.v. hpGHRH 1–44 (Bissendorf Peptides) diluted to 10 ml with isotone saline. Growth hormone was measured by radioimmunoassay (Tandem β-HGH, Hybritech, Liege, Belgium). Intra-assay and interassay coefficients of variation were 3.8 and 5.2% (at 8.1 and 7.8 ng/ml, respectively). The minimum detectable concentration was 0.2 ng/ml. All the data in the text, tables, and figures are presented as means ± SE. Linear regression and correlation, analysis of variance, and unpaired Student's *t* test were used for statistical analysis.

RESULTS

Basal GH values and GH levels after stimulation with hpGHRH 1–44 are shown in Table 2 and Fig. 1. Basal GH levels were not significantly different (Table 2). Growth hormone responses to hpGHRH (ΔGH = peak value − basal value) in type I and type II diabetic patients were slightly lower in patients with NPDRP and PDRP than in patients without DRP; however, the differences did not reach statistical significance when evaluation was performed by analysis of variance (Table 2, Fig. 1). The ΔGH was significantly higher in type I diabetic patients without DRP compared with matched controls ($P < .05$, analysis of variance), whereas GH responses to hpGHRH in type I diabetic patients with NPDRP and PDRP were not significantly different from nondiabetic subjects. Growth hormone levels after hpGHRH in type II diabetic patients without DRP, with NPDRP, and with PDRP were not significantly different from matched controls. In type I and type II diabetic patients, no correlation between diabetes duration, fasting plasma glucose, HbA_{1c}, and ΔGH could be established. The ΔGH was significantly higher in type I than in type II diabetic patients regardless of the presence or absence of DRP ($P < .005$ in patients without DRP and with NPDRP; $P < .0025$ in patients with PDRP).

DISCUSSION

Our data demonstrate that GH responses to hpGHRH 1–44 are not increased in patients with DRP compared with patients without this complication, whereas the increase of GH after GHRH was significantly higher in type I diabetic patients without DRP than in matched controls. Growth hormone responses to hpGHRH are influenced by age (11) and obesity (12). Thus, the decreased GH responses to hpGHRH in type II compared with type I diabetic patients might be explained by the higher age and comparatively modest overweight of the type II diabetic patients.

Our data agree with those of Holland and co-workers (5) who did not find a correlation between GH responses to levodopa and the presence or absence of DRP. In contrast, Kaneko et al. (7) reported increased GH responses to hpGHRH in patients with DRP. Kaneko did not differentiate between patients with type I and type II diabetes mellitus. We studied Caucasians, whereas Kaneko et al. investigated Japanese patients; however, there is still no evidence that GH responses are different in various populations. In our

TABLE 2
Basal growth hormone (GH) levels and GH responses to human pancreatic GH-releasing hormone 1–44 (ΔGH) in type I and type II diabetic patients subdivided into groups of patients without diabetic retinopathy (DRP), with nonproliferative diabetic retinopathy (NPDRP), and proliferative diabetic retinopathy (PDRP), and matched controls

	Without DRP	With NPDRP	With PDRP	Controls
Type I/basal GH (ng/ml)	2.5 ± 1.3 (12)	1.5 ± 0.4 (11)	1.6 ± 0.5 (10)	1.8 ± 0.9
Type II/basal GH (ng/ml)	1.0 ± 0.4 (16)	0.5 ± 0.1 (8)	1.9 ± 0.8 (6)	0.8 ± 0.3
Type I/ΔGH (ng/ml)	25.4 ± 6.9 (12)*	16.9 ± 3.6 (11)*	11.9 ± 2.8 (10)†	8.3 ± 2.0
Type II/ΔGH (ng/ml)	5.1 ± 1.7 (16)*	3.6 ± 0.9 (8)*	1.2 ± 0.8 (6)†	2.6 ± 0.8

Numbers in parentheses equal number of subjects.
ΔGH in type I vs. ΔGH in type II: *$P < .005$ and †$P < .0025$.

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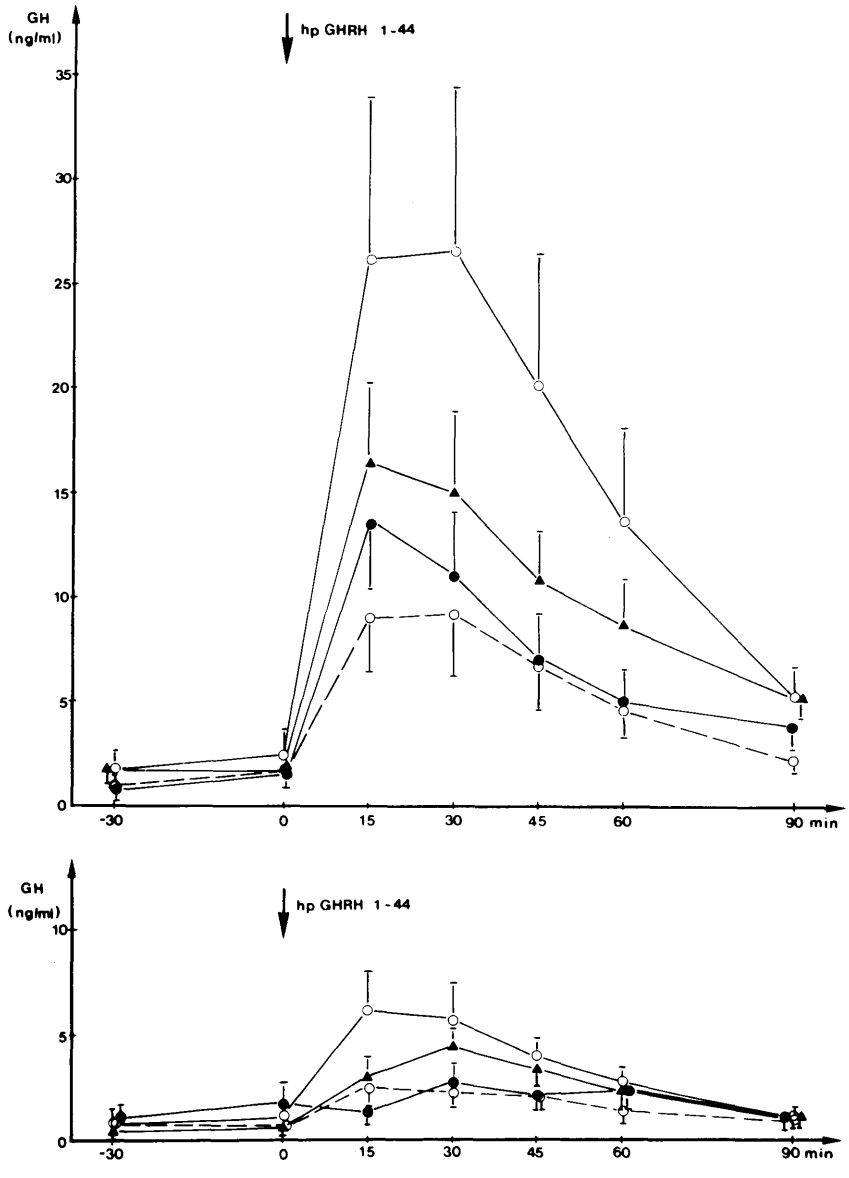

FIG. 1. Growth hormone (GH) responses (mean ± SE) to human pancreatic GH-releasing hormone (hpGHRH 1–44) in type I (*upper panel*) and type II (*lower panel*) diabetic patients, subdivided into patients without diabetic retinopathy (DRP) (○), with nonproliferative DRP (▲) and with proliferative DRP (○) and matched controls (○---○).

patients with DRP, duration of disease was longer than in patients without DRP, whereas the patients of Kaneko et al. with DRP had a significantly shorter diabetes duration than patients without DRP. Because the prevalence of DRP is low in patients with short duration of disease and increases with diabetes duration (13), the results of Kaneko et al. do not seem to be representative for diabetic patients. We do not feel that GH responses to hpGHRH are influenced by the duration of disease, because in type I and type II diabetic patients, no correlation between ΔGH and duration of disease could be established. Because diabetic autonomic neuropathy is to be expected more frequently in patients with severe microangiography (14), GH responses to hpGHRH in patients with DRP may be influenced by diabetic autonomic neuropathy. Hilsted and co-workers reported that in diabetic autonomic neuropathy, GH responses to exercise are blunted (15), whereas no significant differences in the responses of cortisol and GH to hypoglycemia were found (16).

In contrast, recent data demonstrate that in type I diabetic patients with short or moderate diabetes duration and DRP, GH responses to exercise are higher in patients with diabetic autonomic neuropathy than in patients without autonomic neuropathy (17). Because neither the study of Kaneko et al. nor our study specifically addressed this question, however, further studies are needed to assess the influence of diabetic autonomic neuropathy on GH responses to hpGHRH. Growth hormone hyperresponsiveness to hpGHRH in our type I diabetic patients without DRP is in line with data demonstrating increased GH responses to stimuli, e.g., arginine (18) and physical exercise (19). In contrast, recent studies did not find increased GH responses to GHRH in patients with type I diabetes mellitus compared with controls (20,21). Because Sharp et al. (21) mainly studied patients with DRP and Press et al. (20) investigated diabetic patients with long-term disease, it can be assumed that many of their patients had DRP. The observed GH hyperresponse to hpGHRH in type I diabetic patients without DRP may be caused by a

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defective regulation of somatostatin secretion, which is also suggested for the well-known phenomenon of failure of glucose-mediated suppression in this disorder (20). The decreasing secretory capacity for the release of GH to hpGHRH stimulation with progressing DRP could be explained by a general microvascular disorder involving the pituitary. Growth hormone responses to hpGHRH in type II diabetic patients were not significantly different from control subjects. Recently, Richards et al. (8) reported an impaired GH response to hpGHRH in patients with type II diabetes mellitus. Because obesity blunts the GH responses to hpGHRH (12), the findings of Richards et al. might be explained by the fact that their type II diabetic patients were more obese than the controls.

Our data show that in type I and type II diabetes, advanced diabetic retinopathy is not associated with increased GH responsiveness to hpGHRH. However, because we demonstrated a GH hyperresponsiveness to hpGHRH in patients with type I diabetes mellitus without DRP, we cannot exclude that GH might influence the development of DRP in the very early stages of the disease. Prospective follow-up studies are thus needed to clarify whether GH indeed plays a role in the pathogenesis of diabetic microangiopathy.

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