Cholinergic control of growth hormone (GH) responses to GH-releasing hormone in insulin dependent diabetics: evidence for attenuated hypothalamic somatostatinergic tone and decreased GH autofeedback

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Summary

OBJECTIVE We have investigated the effects of cholinergic modulation with pirenzepine and pyridostigmine and of GH pretreatment on the subsequent GH response to a maximal stimulatory dose of GH-releasing hormone (GHRH) in patients with insulin dependent diabetes mellitus (IDDM). We have also investigated the relationship between the differences in metabolic control and other parameters of disease state with the differences in GH responses in IDDM.

PATIENTS Thirteen male subjects with IDDM and no clinical evidence of complications were selected based on HbA, levels to provide a wide range of metabolic control. Seven normal subjects were also studied.

DESIGN Twelve of the subjects with IDDM and six normal subjects received pirenzepine 200 mg and pyridostigmine 120 mg pretreatment 60 minutes and GH pretreatment 3 hours before an i.v. injection of GHRH (1-44) (80 μg) in random order. All subjects underwent a control study with GHRH alone.

MEASUREMENTS Serum GH and plasma glucose were measured at regular intervals throughout the study. Fasting plasma glucose and HbA, were measured before each study to provide measures of metabolic control.

RESULTS Subjects with IDDM demonstrated exaggerated GH responses to GHRH compared to normals. Pirenzepine significantly reduced GH responses in both normal and diabetic subjects. However, the GH response to GHRH after pirenzepine was higher in subjects with IDDM (mean GH: IDDM vs normals; 8.1 ± 1.3 vs 2.9 ± 0.7 μU/l, P < 0.05). Pyridostigmine 120 mg significantly augmented the GH response to GHRH in normal subjects. In diabetic subjects, pyridostigmine failed to increase GH response to GHRH compared to GHRH alone (mean GH: pyridostigmine vs control: 75.7 ± 12.6 vs 38.9 ± 5.4 μU/l, P = NS). GH responses to GHRH after pyridostigmine pretreatment in both normal and diabetic subjects did not differ and the GH response to GHRH after pyridostigmine in normal subjects did not differ from the GH response to GHRH alone in diabetic subjects. In normal subjects, GH pretreatment significantly reduced subsequent GH responsiveness to GHRH (Δpeak GH 26.4 ± 5.2 vs 7.7 ± 5.4 μU/l, P < 0.04). In contrast, GH pretreatment did not cause any significant reduction in GH responsiveness to GHRH in diabetics (Δpeak GH 53.6 ± 9.7 vs 33.4 ± 11 μU/l, P = NS). No significant correlation was demonstrated between measures of diabetic control and the responses to GHRH alone or after cholinergic modulation and GH pretreatment.

CONCLUSION These data suggest that ambient hypothalamic cholinergic tone in diabetes is high, and of similar degree to the enhanced cholinergic tone in normal subjects pretreated with pyridostigmine. We suggest that in diabetic subjects, the reduced responsiveness to autautofeedback may be secondary to the enhanced cholinergic tone demonstrated in these patients. The mechanisms linking the uncontrolled diabetic state to this abnormal neuroregulation of GH remains unknown at present.

Elevated growth hormone (GH) levels despite hyperglycaemia have been repeatedly documented in patients with IDDM since the original reports (Hansen, 1970). These patients are also known to have abnormalities in GH neuroregulation. Despite elevated blood glucose levels, they show higher mean 24 hour GH levels than normal (Hayford et al., 1980), together with exaggerated GH responses to physiological and pharmacological stimuli (Burday et al., 1968; Hansen, 1970; Ajlouni et al., 1975; Speroni et al., 1983; Krassowski et al., 1988).

The cause of abnormal GH secretion in IDDM is not known but hypothalamic dysfunction is at least one potential mediator. An exaggerated GH response to growth-hormone releasing hormone (GHRH) in IDDM reported by several groups (Krassowski et al., 1988; Schaper et al., 1990b) is...
consistent with reduced somatostatinergic tone in IDDM. Several studies have related the problem to poor glycaemic control. Tamborlane et al. (1979) showed that GH secretion may be normalized after a period of improved diabetic control in IDDM. Others have demonstrated either unchanged (Herschcopf et al., 1982; Hermansen et al., 1987) or increased (Wurzburger et al., 1990) spontaneous GH secretion after sustained normoglycaemia.

Recent data have highlighted the fundamental importance of hypothalamic cholinergic pathways in the control of GH release in man (Dieguez et al., 1988). Cholinergic blockade with drugs such as atropine or pirenzepine abolishes the GH response to all known GH secretagogues (including arginine, t-dopa, exercise, glucagon and growth hormone releasing hormone (GHRH)) (Massara et al., 1984; Jordan et al., 1986; Delitala et al., 1987), with the exception of insulin induced hypoglycaemia (Evans et al., 1985). Cholinergic muscarinic receptor blockade also abolished physiological GH release, including slow-wave sleep related GH release and the GH response to food and to exercise (Peters et al., 1986; Page et al., 1989).

Conversely, enhancement of endogenous cholinergic tone with pyridostigmine enhances both basal and GHRH stimulated GH release (Massara et al., 1986a; Ross et al., 1987b).

GH secretion is inhibited by prior administration of GH both in man (Hagen et al., 1972; Mendelson et al., 1981; Rosenthal et al., 1986) and in laboratory animals (Wulloughby et al., 1980; Abe et al., 1983). This negative feedback is probably effected both directly by GH in the acute setting (Ross et al., 1987a) and indirectly through insulin-like growth factor 1 (IGF-1) in the more chronic setting. IGF-1 inhibits GH secretion at hypothalamic level by stimulating hypothalamic secretion of somatostatin and also directly at pituitary level (Berelowitz et al., 1981b). Direct GH effects on GH secretion are mediated by increased hypothalamic somatostatin secretion (Ross et al., 1987b) which in turn is under tonic inhibitory cholinergic control (Dieguez et al., 1988). The presence of a raised hypothalamic cholinergic tone in IDDM may affect the autoregulation of GH on its own secretion, thus providing another mechanism for GH hypersecretion in these patients.

In this study we have investigated the effect of cholinergic modulation and exogenous GH administration on the GH response to a maximal stimulatory dose of GHRH in IDDM. We have also attempted to relate the differences in responses to GHRH with various parameters of disease state.

### Materials and methods

We have studied seven normal subjects and 13 patients with IDDM whose characteristics are listed in Table 1. The diabetic patients had no clinical evidence of diabetic complications or microalbuminuria. The normal subjects had no family history of diabetes or other endocrinopathy and no subject was taking any medication other than insulin for diabetes. Only male subjects were selected for the study as there is a sex related difference in the neuroregulation of GH secretion that may be related to altered cholinergic tone (Barbarino et al., 1991). Each patient gave informed consent for participation in the study that was approved by the local hospital Ethical Committee.

The study consisted of four experiments performed in random sequence and separated by intervals of at least a week. On the day before each test, each diabetic patient received his last dose of insulin in the evening and no further insulin was administered until the end of the test on the following day. After an overnight fast, each subject was admitted to the Investigation Unit and to avoid differences due to diurnal variation in endogenous secretion of GHRH or somatostatin, the GHRH stimulus was given at the same clock time in all four experiments. Each subject rested in a recumbent position and a 30-minute period was allowed for stabilization after venupuncture. The catheter was kept patent by a slow saline infusion. Each subject underwent all four experiments except for one diabetic and one normal subject who underwent only study 1:

| Table 1 Clinical characteristics of patients |
|-----------------|-----------------|----------------|-----------------|----------------|
| Patient         | Age (years)     | BMI (kg/m²)   | Duration of disease (years) | Mean HbA₁ (%) |
| IDDM            | Mean ± SE 36.5 ± 2.1 | 26.3 ± 0.5 | 16.1 ± 1.8 | 10.86 ± 0.49 | 13.23 ± 1.48 |
| Range           | 25-48           | 22.6-29.2     | 8-26            | 8.27-14.80   | 5.32-22.40   |
| Normal subjects | Mean ± SE 32.7 ± 2.3 | 25.2 ± 0.8 | 23.3-29.5 | |

### References

Dieguez et al. (1988); Massara et al. (1984); Jordan et al. (1986); Delitala et al. (1987); Herschcopf (1987); Wurzburger et al. (1990); Peters et al. (1986); Page et al. (1989); Hagen et al. (1972); Mendelson et al. (1981); Rosenthal et al. (1986); Wulloughby et al. (1980); Abe et al. (1983); Ross et al. (1987a); Ross et al. (1987b); Berelowitz et al. (1981b); Barbarino et al. (1991).
(1) Intravenous injection of 80 μg GHRH (1-44) (Sanofi, UK) at 1130 h alone.
(2) 200 mg oral pirenzepine (PIR) (cholinergic muscarinic antagonist) (Gastrozepine, Boehringer, Italy) at 1030 h followed by intravenous injection of 80 μg GHRH (1-44) at 1130 h.
(3) 120 mg oral pyridostigmine (PD) (acetyl cholinesterase inhibitor) (Mestinon, Roche, Switzerland) at 1030 h followed by intravenous injection of 80 μg GHRH (1-44) at 1130 h.
(4) Intravenous injection of 2 IU recombinant human GH (Norditropin, Novo Nordisk, Sweden) at 0830 h followed by an intravenous injection of 80 μg GHRH (1-44) at 1130 h.

Samples were taken every 15 minutes for GH and every 30 minutes for glucose from 15 minutes before the start of the study to 2 hours after the administration of GHRH. Samples were also taken from patients for haemoglobin A1c (HbA1c) before the start of all four experiments. All samples for GH were separated immediately and serum stored at -20°C before being assayed. The arithmetic means of fasting plasma glucose and HbA1c were used as indices of metabolic control of the patients.

Plasma glucose was measured by a glucose oxidase method (Yellow Springs Analyser). HbA1c was measured by Corning agar electrophoresis method (Corning Ltd, UK). The normal range was 5-8%. Serum GH was measured using a commercial two-site immunoradiometric assay (Omnia GH IRMA kit, Immunodiagnostic Systems Ltd). Intra-assay coefficient of variation (CV) was 5%; interassay CV was 10%; sensitivity limit of the assay was 0.3 mU/l. Samples were assayed in duplicate.

**Statistical analysis**

The GH secretory responses were expressed as peak absolute value (mU/l), and mean GH levels (mU/l). As exogenous GH administration tended to suppress basal GH levels, effects of exogenous GH administration were analysed by using mean ΔGH and Δpeak GH levels (mU/l). ΔGH levels are calculated by subtracting the mean of GH levels at -15 and 0 min before GHRH injection from absolute GH levels at the individual time points. Because of the positively skewed distribution of GH levels after PD pretreatment in a normal population, the summary measures (peak GH and mean GH levels) after PD and PIR pretreatment and after control study were log transformed prior to statistical analysis. Comparisons of the log transformed summary measures were performed by two-sample t-test (Matthews et al., 1990). Untransformed values were used for analysis of effects of GH autofeedback as similar results were obtained using either log transformed or untransformed figures. Linear regression analysis was used where appropriate. Multivariable regression analysis was used to determine the relationship between the differences in GH responses and the mean fasting plasma glucose and HbA1c. \( P < 0.05 \) was considered statistically significant. All values are expressed as mean±SEM.

**Results**

Baseline GH levels during studies 1–3 did not differ within either diabetic or normal patient groups. However, baseline GH levels were significantly higher in IDDM patients on all three study days when compared to the normal subjects (Table 2) \( P < 0.05 \). After GHRH alone, the mean peak GH level was reached after 15 minutes in both normal and diabetic subjects. The mean peak GH level and mean GH levels.
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Table 3 GH responses to GHRH (1–44) alone (Study 1) and to GHRH (1–44) after GH pretreatment (Study 4) in diabetic and normal subjects. Results are expressed as mean ± SEM

<table>
<thead>
<tr>
<th>Summary measure</th>
<th>IDDM</th>
<th>Normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre GHRH baseline (mU/l)</td>
<td>14.7 ± 4.8</td>
<td>18 ± 4.4</td>
</tr>
<tr>
<td>Post GHRH Δpeak GH (mU/l)</td>
<td>24.3 ± 8.5</td>
<td>26.4 ± 5.2</td>
</tr>
<tr>
<td>Post GHRH mean ΔGH (mU/l)</td>
<td>25.8 ± 4.6</td>
<td>15.0 ± 3.5</td>
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Study 4

| Pre GH baseline (mU/l)       | 7.9 ± 5.2   | 2.1 ± 0.6  |
| Pre GHRH Δpeak GH (mU/l)    | 17.4 ± 1.9  | 161.2 ± 8.5 |
| Pre GHRH mean ΔGH (mU/l)    | 5.8 ± 6.9   | 31.7 ± 2.6  |
| Pre GHRH baseline (mU/l)     | 5.8 ± 1.9   | 1.3 ± 0.1  |
| Post GHRH Δpeak GH (mU/l)   | 33.4 ± 10.8 | 7.7 ± 5.4  |
| Post GHRH mean ΔGH (mU/l)   | 15.8 ± 4.1  | 3.7 ± 2.6  |

Administration of PIR 200 mg significantly reduced the GHRH-induced GH increase in both diabetic and normal subjects (Table 2, Fig. 2). The GH response to GHRH after PIR was significantly lower in normal subjects compared to diabetic subjects when the mean GH levels were compared although the difference was not significant when peak values were compared (Table 2, Fig. 2). Administration of PD 120 mg significantly augmented the GHRH-induced GH increase in normal subjects (Fig. 2). However, in diabetic subjects PD did not significantly increase the GH response to GHRH compared to GHRH alone. Furthermore, the GH response to GHRH after pretreatment with PD in diabetic subjects was not significantly different from that in normal subjects when peak GH or mean GH values were compared. Also, the GH response to GHRH after pretreatment with PD in normal subjects was not significantly different from the GH response to GHRH alone in the diabetic subjects when the same measures were compared (Table 2, Fig. 2).

Baseline GH levels tended to be suppressed after GH pretreatment in diabetics but not significantly so (Table 3). In Study 4, GH levels peaked at 15 minutes after GH injection in both groups. The pre-GHRH Δpeak GH levels for both groups were not significantly different. The mean ΔGH prior to the GHRH injection was significantly higher in the diabetic groups. However, regression analysis between GH summary measures (Δpeak GH and mean ΔGH) prior to GHRH administration against GH summary measures (Δpeak GH and mean ΔGH) after GHRH administration did not reveal significant results. Three hours after the GH injection, GH levels returned to levels not significantly different from those before the GH injection (Table 3). In normal subjects, GH pretreatment significantly reduced the subsequent GH response to GHRH (Fig. 3). Two of the levels were significantly higher in diabetic subjects (Table 2, Fig. 1). Correlation analyses of either peak GH or mean GH levels with mean fasting plasma glucose, mean HbA1c, basal GH level, age, duration of disease or body mass index showed no significant associations.

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Fig. 2 a. Mean serum GH levels (mean ± SEM) and b. serum GH peaks (mean ± SEM) elicited by GHRH (1–44) 80 μg given after □, pirenzepine 200 mg and ■, pyridostigmine 120 mg or □, after GHRH alone. NS, Not significant. Y-axis is drawn to a logarithmic scale.

Fig. 3 GH response to GHRH (1–44) 80 μg ●, alone or ▲, after GH pretreatment in a. diabetic subjects and b. normal subjects.

Fig. 4 a. The Δpeak and b. mean ΔGH of the GH response to GHRH (1–44) 80 μg ■, alone and □, after GH pretreatment in diabetic and normal subjects.
normal subjects failed to respond to GHRH after the GH pretreatment. On the other hand, all the diabetic subjects responded to GHRH after GH pretreatment which did not cause any significant reduction in GH responsiveness to GHRH (Table 3, Fig. 3). After GH pretreatment, GH responses to GHRH in diabetic subjects remained significantly higher than in normal subjects (Table 3, Fig. 4).

Correlation analysis of peak GH, mean GH or percentage change of GH response with mean fasting plasma glucose, mean HbA1c, basal GH levels, age, duration of disease or body mass index did not provide any meaningful associations in studies 2 and 3 (data not shown). No association was noted between the fasting plasma glucose and GH responses (as measured by peak GH and mean GH levels) on each study day in studies 1, 2 and 3. Nor was there any association between GH summary measures (Δpeak GH and mean ΔGH) and the above parameters in study 4 (data not shown). Similarly, no association was noted between plasma glucose at the time of GHRH injection and subsequent GH responsiveness to GHRH as measured by Δpeak GH and mean ΔGH.

Plasma glucose did not change significantly from the fasting level during all the studies in diabetic subjects (data not shown). Four of the diabetic subjects and four normal subjects experienced transient flushing after GHRH administration. PIR caused dry mouth in eight diabetic subjects and five normal subjects and transient impairment of visual accommodation in three diabetic and five normal subjects. PD caused the expected cholinergic symptoms of borborygmi in six diabetic and three normal subjects and abdominal cramps in a further four diabetic and three normal subjects. Excessive lacrimation occurred in five diabetic and one normal subject while excessive salivation occurred in three diabetic and one normal subject. One diabetic and one normal subject suffered fasciculation of the tongue with transient dysarthria.

Discussion

Diabetic patients have higher mean daily GH concentrations than normal subjects (Hayford et al., 1980). The high basal GH levels in our diabetic subjects is consistent with other reports. They also have exaggerated GH responses to a variety of stimuli (Burday et al., 1968; Hansen, 1970; Ajlouni et al., 1975; Speroni et al., 1983; Krassowska et al., 1988). The mechanism underlying GH hypersecretion in IDDM remains controversial. Recent evidence is consistent with the view that hypothalamic dysfunction is at least one potential mediator, with reduced hypothalamic somatostatin release being the most likely explanation. In normals, acute hyperglycaemia inhibits GHRH stimulated GH secretion probably by inducing hypothalamic somatostatin secretion (Penalva et al., 1989). In diabetic subjects, the GH responses to GHRH (Sharp et al., 1984) and exercise (Ismail et al., 1991) during periods of hyperglycaemia were not significantly different from those during periods of euglycaemia maintained by the euglycaemic clamp technique. This suggests that in IDDM, hyperglycaemia is not able to stimulate somatostatin secretion as effectively as in normals. Asplin et al. (1989) noted an increased frequency of GH pulses and enhanced interpulse GH concentration in IDDM again suggesting a diminished somatostatin tone. In our study, the GH response to GHRH was increased compared to normal subjects confirming previous findings (Krassowski et al., 1988; Schaper et al., 1990b). Since the dose of GHRH used in the study is a maximal stimulatory dose (Penalva et al., 1990), this finding is consistent with a defect in hypothalamic somatostatin secretion.

In agreement with previous findings (Pietschmann et al., 1986), our data confirm that cholinergic muscarinic blockade with PIR greatly suppresses GH responses to GHRH in both normal and diabetic subjects. Using the same dose of PIR, the GH response to GHRH in diabetic subjects was still significantly higher than that in normal subjects in our study consistent with a decreased sensitivity to muscarinic cholinergic receptor blockade (Coiro et al., 1990).

Our data also confirm the previous finding that enhancement of the endogenous cholinergic tone by PD greatly enhances GH responses to GHRH in normal subjects (Massara et al., 1986a; Ross et al., 1987b; Penalva et al., 1990). In contrast to normal subjects, however, pretreatment with PD did not lead to enhancement of the GH response to GHRH in diabetic subjects. In a similar study, Giustina et al. (1990) showed that only IDDM subjects with an exaggerated GH response to GHRH had an impaired response to PD. This subgroup was subsequently shown to have poorer metabolic control and longer duration of disease. However, Giustina et al. (1990) studied both males and females together. This may partly explain the difference in the findings as a sex related difference in the neuroregulation of GH secretion that may be related to altered cholinergic tone has been demonstrated in humans (Barbarino et al., 1991). In contrast, our study showed that the diabetic subjects as a group had an exaggerated response to GHRH and impaired response to PD and that this difference could not be explained by differences in degree of metabolic control or duration of disease despite our selection of patients with a wide range of metabolic control (HbA1c range 8.27-14.8%) and duration of disease (range 8-26 years) (see below). The GH responses to GHRH after pretreatment with PD in both normal and diabetic subjects did not differ and the GH response to GHRH after PD pretreatment in normal subjects
did not differ from the GH response to GHRH alone in diabetic subjects. These data suggest that the level of hypothalamic cholinergic tone in diabetic subjects was similar to the enhanced cholinergic tone seen in normal subjects pretreated with PD. Thus pretreatment of the diabetic subjects with PD was not able to increase further the already elevated cholinergic tone present in these patients.

In this study, despite the presence of hyperglycaemia, the GH response to GHRH in IDDM was still greater than in normal subjects where a similar degree of hyperglycaemia suppresses GH response to GHRH (Davis et al., 1984). In normal subjects glucose inhibits the GH response to GHRH probably by stimulating hypothalamic somatostatin secretion (Penalva et al., 1989). It has been suggested that glucose acts on somatostatinergic neurones via a different pathway to PD (Delitala et al., 1990). Thus the enhanced cholinergic tone in IDDM demonstrated here could be responsible for the apparent insensitivity of somatostatinergic neurones to hyperglycaemia in IDDM.

Our data show that GH pretreatment prior to the GHRH stimulus significantly suppressed subsequent GH responses to GHRH in normal subjects. This confirms previous studies (Ross et al., 1987a; Schaper et al., 1990a) which also showed that the inhibition of GH responses to GHRH were not mediated by IGF-1.

The mechanism of the direct effect of exogenous GH on the GH response to GHRH has been suggested to be via hypothalamic somatostatin as a part of the GH autoregulation loop (Tannenbaum, 1980; Berelowitz et al., 1981a; Torsello et al., 1988). Recent evidence indicates an important functional link between hypothalamic cholinergic and somatostatinergic pathways in the mediation of GH autoregulation (Massara et al., 1986b; Ross et al., 1987b) although direct GH effects and cholinergic effects may exert their opposing effects on GH secretion via separate inputs to hypothalamic somatostatin (Kelijman & Frohman, 1991).

In our study, exogenous GH did not inhibit subsequent GH responses to GHRH in diabetic subjects to the same degree as in normals. This suggest that in IDDM, the stimulatory effect of GH on hypothalamic somatostatin secretion is decreased, although a primary defect in the pituitary responses to somatostatin, cannot be excluded (Cohen & Abplanalp, 1991). Schaper et al. (1990a) demonstrated a significant suppression of GH response to GHRH after GH pretreatment in diabetic subjects although the GH response was increased and less inhibited in the diabetic subjects compared to normal subjects. However, all the patients were treated with continuous s.c. insulin infusion and had basal insulin infusion throughout the study. In another study, Giustina et al. (1991) demonstrated that GH pretreatment was not able to inhibit the GH response to GHRH in a subgroup of their diabetic population compared to the normal subjects. However, a control study with GHRH alone was not done in their diabetic subjects. Furthermore, both male and female subjects were studied together.

The mechanism of possible reduced hypothalamic responsiveness to GH in IDDM is at present unknown. This study suggests that IDDM patients have a raised hypothalamic cholinergic tone and since somatostatin release is under tonic cholinergic inhibition (Dieguez et al., 1988), the result would be reduced somatostatin release. In the model suggested by Kelijman and Frohman (1991), GH would act on a hypothalamic receptor (Harvey et al., 1990) to stimulate somatostatinergic neurones whilst cholinergic neurones would inhibit somatostatinergic neurones via a different pathway. In diabetic subjects, GH acting on its receptor in the hypothalamus is not able to overcome the raised inhibitory cholinergic tone acting on the somatostatinergic neurones. This would explain its inability to stimulate somatostatin release and thus to induce its own feedback inhibition as effectively as in normal subjects.

Controversy persists regarding the role of metabolic control in the genesis of the altered neuroregulation of GH in IDDM. GH secretion may be normalized after a period of improved diabetic control (Tamborlane et al., 1979), be unchanged (Hershcopf et al., 1982; Arias et al., 1984; Hermansen et al., 1987) or be increased (Wurzburger et al., 1990). The relationship between degree of metabolic control and response to GHRH in diabetics is also unclear, some authors indicating correlation between HbA1c and GHRH-induced GH secretion (Giustina et al., 1990) while others did not (Sharp et al., 1984; Krysowski et al., 1988; Schaper et al., 1990b). In our study, diabetic subjects were selected initially to provide as wide a range of metabolic control as possible. Fasting plasma glucose and HbA1c were repeated during the study period. There was no correlation between these measures and basal GH or the response to GHRH alone or after PIR, PD or after GH pretreatment. No correlation was demonstrated between duration of disease, age and basal GH levels and GH responses to GHRH alone or after cholinergic modulation, or between body mass index and the GH responsiveness.

In addition to altered GH autoregulation, patients with IDDM also demonstrate an altered feedback by IGF-1 (Schaper et al., 1990a). As IGF-I exerts its negative feedback by stimulating somatostatin secretion (Berelowitz et al., 1981b), it is possible that this reduced stimulation of somatostatin release by IGF-1 in IDDM may be related to the high cholinergic tone in these patients although IGF-I
also has a direct effect on the pituitary. In addition, patients with IDDM also have high levels of IGF-I binding protein 1 (IGF-BP1) (Holly et al., 1988) which may inhibit receptor binding of IGF-I. The IGF-I level itself is either normal or suppressed in IDDM (Amiel et al., 1984) contributing to the blunted IGF-I feedback on GH secretion in these patients.

In conclusion, our data indicate that cholinergic augmentation with pyridostigmine does not increase GH responses to GHRH in diabetic patients in contrast to normals, while cholinergic blockade with pirenzepine reduced GH responses to GHRH but not to the same extent as in normals. These observations are consistent with increased intrinsic activity of hypothalamic cholinergic neurones which in turn would lead to a reduced somatostatin release and relative GH hypersecretion in diabetic subjects. We have also demonstrated that GH pretreatment was not able to inhibit subsequent GH responsiveness to GHRH in IDDM to the same degree as in normal subjects. We suggest that this unresponsiveness to GH autoregulation is related to a high cholinergic tone which may be present in these patients. The decreased hypothalamic sensitivity to GH may represent one of the factors responsible for the GH hypersecretion in IDDM. The mechanisms linking the uncontrolled diabetic state to this abnormal neuroregulation of GH remain unknown at present.

References


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