Growth hormone, prolactin and thyrotrophin responses to thyrotrophin-releasing hormone in diabetic patients

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Summary

Growth hormone (GH), prolactin (PRL) and thyrotrophin (TSH) responses to thyrotrophin-releasing hormone (TRH) were studied in 15 insulin-dependent diabetic patients. Basal plasma GH levels were raised above 5 $\mu\text{u./l}$ in 6 patients and following the injection of TRH there was a significant rise in plasma GH levels in 9. The mean rise in plasma GH from basal to peak values was significant in the group as a whole ($P < 0.01$).

Basal PRL and TSH levels were normal and rose normally in response to TRH.

GH release may be qualitatively abnormal in some diabetics and any such loss of specificity of GH-releasing mechanisms would further contribute to the raised GH levels found in many diabetics which would be of importance if GH is a factor in the aetiology of diabetic microangiopathy.

Introduction

In insulin-dependent diabetics, plasma growth hormone (GH) levels are usually elevated and show more frequent and higher peaks compared with non-diabetics (Hansen and Johansen, 1970; Corral *et al.*, 1974). Plasma GH levels are also raised more easily in diabetics by stimuli such as exercise (Hansen, 1970, 1971), arginine (Passa, Rousselie and Ganville, 1977) and glucagon (Waldhauser *et al.*, 1976). These quantitative differences in GH responses may partly explain the raised plasma GH levels in diabetics, but, in addition there may be qualitative differences in GH release as occurs in anorexia nervosa (Maeda *et al.*, 1976; Harrower *et al.*, 1977b) and chronic renal failure (Gonzalez-Barcena *et al.*, 1973; Czernikow *et al.*, 1976) where plasma GH levels are also often raised. In these conditions, thyrotrophin-releasing hormone (TRH) may stimulate GH release, an effect which does not occur in normal subjects, but which is similar to that reported in acromegalic patients (Irie and Tsushima, 1972; Luizzi *et al.*, 1974; Gomez-Pan *et al.*, 1975; Harrower *et al.*, 1977a). If a similar effect occurs in diabetics then this would contribute further to GH release, ensuring that diabetic patients are exposed

to high plasma GH levels for considerable periods of time.

To determine whether GH release in diabetics is modified by TRH, the author studied the effect of this hormone on plasma GH levels in a group of insulin-dependent diabetics. The effect of TRH on plasma prolactin (PRL) and thyrotrophin (TSH) levels was also investigated to ensure that an adequate stimulus had been given and also to determine whether PRL and TSH were released normally in response to this stimulus in such patients.

Patients and methods

Fifteen insulin-dependent diabetic patients (9M and 6F) gave informed consent to the study. All were hospital in-patients at the time and clinical details are shown in Table 1. After an overnight fast an intravenous butterfly needle (Abbott) was inserted into a forearm vein at least 30 min before blood sampling began: the needle was kept patent with heparinized saline. In each patient, after a baseline sample had been taken, 500 μg TRH (Roche) was injected and further blood samples taken after 20, 30, 60 and 90 min. Plasma was separated and stored at -20°C for later analysis. All specimens were assayed for GH (Schalch and Parker, 1964), TSH (Irvine *et al.*, 1973) and PRL (Reuter *et al.*, 1976) by radioimmunoassay and for glucose with a Technicon autoanalyser using a glucose oxidase method. For the purposes of the study a 2-fold or greater rise in plasma GH was considered significant.

Results

Basal plasma GH levels were raised above 5 $\mu\text{u./l}$ in 6 patients (Table 2, nos 1, 4, 7, 10, 11 and 13). Following the injection of TRH, plasma GH levels rose significantly in 9 patients (nos 1-5, 8, 9, 12 and 15). The rise in plasma GH from basal to peak levels was significant in the group as a whole ($P < 0.01$) (Fig. 1) and the mean ($\pm$ s.e. mean) values at each time of sampling are shown in Fig. 2 and Table 2.

Basal plasma PRL levels were normal in all 15

TABLE 1. Clinical data regarding age, sex, duration of diabetes and presence of complications in 15 diabetic patients

Patient	Sex	Age (years)	Duration of diabetes (years)	Proliferative retinopathy	Other diabetic complications
1	M	19	4	—	—
2	M	30	17	+	Peripheral vascular disease, Autonomic neuropathy
3	M	50	25	+	Peripheral vascular disease, Autonomic neuropathy
4	F	17	7	—	—
5	F	19	<1	—	—
6	M	30	4	—	—
7	F	15	5	—	—
8	M	22	4	—	—
9	F	58	2	—	—
10	M	42	<1	—	Background retinopathy
11	M	44	12	—	Background retinopathy
12	M	15	3	—	—
13	F	62	11	—	Background retinopathy, Somatic neuropathy
14	M	35	24	+	Peripheral vascular disease
15	F	18	7	—	—

FIG. 1. Basal and peak plasma GH levels (mu./l) in 15 diabetic patients before and after injection of TRH 500 µg.

patients and rose normally in response to TRH (Fig. 3).

Basal TSH levels were also normal in all 15 patients and rose normally in response to TRH (Fig. 4).

FIG. 2. Mean $\pm$ s.e. mean plasma GH level (mu./l) in 15 diabetic patients before and after injection of TRH 500 µg.

Blood glucose levels ranged from 63–443 mg/dl (3.5–24.5 mmol/l), but did not change significantly in any patient during the procedure.

Discussion

The role of GH in the pathogenesis of diabetic microangiopathy has been debated since Houssay and Biassoti (1930) showed that hypophysectomy ameliorated diabetes. Pituitary ablation has been used to treat severe retinopathy with some success (Luft, Olwercroner and Sjögren, 1955; Joplin *et al.*, 1965; Cullen *et al.*, 1971; Kohner *et al.*, 1976),

and Lundbaek *et al.* (1970, 1971) have suggested a causal relationship between GH and the development of retinopathy in diabetics. This is also suggested by the report that retinopathy is worsened when GH is administered to pituitary-ablated patients (Ray *et al.*, 1968). Secretion of GH is abnormal in some diabetics, plasma levels being elevated with more frequent and higher peaks compared to normal subjects (Corral *et al.*, 1974). In addition, the patterns of GH response to different stimuli such

as exercise (Hansen, 1970; 1971), glucose loading (Knopf *et al.*, 1973), arginine (Passa *et al.*, 1977), glucagon (Waldhausl *et al.*, 1976) and the suppressive effect of TRH on L-dopa-promoted GH release (Dølva, Torjesen and Hanssen, 1976) are normal in diabetics. It is also possible that in diabetes there is an altered sensitivity in the mechanism for GH release which allows various stimuli either to produce an exaggerated pattern of GH release or, as with TRH, to promote release of GH, an effect which does not occur normally.

FIG. 3. Mean $\pm$ s.e. mean plasma PRL levels (mu./l) in 15 diabetic patients before and after injection of TRH 500 μ g.

FIG. 4. Mean $\pm$ s.e. mean plasma TSH levels (mu./l) in 15 diabetic patients before and after injection of TRH 500 μ g.

TABLE 2. Plasma GH levels (mu./l) in 15 diabetic patients before and after injection of TRH 500 μ g

Patient	Time (min) after TRH			
	0	30	60	90
1	5.34	10.7	35.3	21.7
2	2.96	3.75	3.4	13.0
3	0.75	0.79	0.75	3.59
4	14.9	6.12	1.15	29.9
5	2.6	5.66	9.33	9.52
6	0.87	0.87	0.87	0.87
7	18.9	32.0	20.9	28.0
8	1.3	1.1	3.12	5.06
9	0.67	2.62	2.07	2.96
10	5.87	5.44	5.46	6.25
11	17.6	13.1	15.4	5.48
12	4.2	6.9	9.9	15.0
13	12.0	11.0	3.2	2.4
14	1.5	2.2	2.3	2.0
15	1.6	3.3	12.0	19.0
Mean	6.07	7.04	8.34	10.98
s.e. mean	1.67	1.97	2.39	2.43

Plasma GH levels were significantly raised above the basal level in response to TRH in 9 patients. The peak response was achieved after 30, 60 and 90 min in one, 2 and 6 patients respectively (Table 2) and, although blood sampling was not continued after 90 min, it is unlikely that a response occurring after this time could be attributed to the effect of TRH. The effect of TRH on GH release appears to be variable and is certainly less definite than on TSH or PRL release. It was not related to the presence of specific diabetic complications or blood glucose levels during the test. While plasma GH levels fluctuate spontaneously in both normal and diabetic subjects it is unlikely that the changes of the magnitude found in these patients could be attributed to this alone. Control plasma GH measurements without TRH injection over the same time period would have clarified this possibility. Previous diabetic control may be important, but reliable information such as that provided by HbA_{1c} levels was not available at the time.

Basal PRL levels and the response to TRH were normal in all 15 patients suggesting that PRL has little part to play in the control of diabetes.

Basal TSH levels and the TSH responses to TRH were also normal, confirming that the stimuli were adequate and that thyroid function was normal.

It appears, therefore, that in some diabetics GH release is qualitatively abnormal and any such loss of specificity of GH-releasing mechanisms could contribute to the raised plasma GH levels found in many diabetics. If GH is a factor in the pathogenesis of microangiopathy (Lundbaek, 1976) then such diabetics would be even more likely to be exposed to high plasma GH levels for long periods of time with adverse consequences.

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