Growth hormone response
to growth hormone-releasing hormone
in normal and uraemic children.
Comparison with hypoglycaemia following
insulin administration

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Abstract. The uraemic syndrome is characterized by several endocrinological disturbances. This study was undertaken in order to evaluate the GH response to growth hormone-releasing hormone (GRH) in children with chronic renal failure (CRF) and to compare the results with those observed after insulin hypoglycaemia. Twenty-two children with CRF, 10 undergoing continuous ambulatory peritoneal dialysis (CAPD) and 12 on conservative treatment (CT), age ranges 2–15 years, were studied and the data were compared with those from 14 children with normal renal function and normal hormonal behaviour, affected by short stature (NC), and those form 13 healthy adult volunteers (NA).

The GRH test (1 μg/kg body weight, iv) was carried out in 8 CAPD, 8 CT, 9 NC and 10 NA subjects. The blood samples were taken every 30 min for 3 h in CAPD and CT and for 2 h in NC and NA starting at 09.00 h. The following hormones were measured: GH, LH, FSH, PRL, TSH and cortisol (F). The insulin test (0.1 U/kg body weight, iv) was carried out in 5 CAPD, 5 CT, 10 NC and 9 NA on blood samples taken every 30 min for 2 h, measuring GH and glycaemia. No adverse effects were observed after the infusion of GRH.

GRH administration induced a prompt response in all subjects, but GH plasma levels were significantly higher in uraemic children than in adults (peak value of 43.5 ± 8.2, 45.0 ± 8.4, 27.8 ± 6.0; 13.5 ± 2.6 μg/ml in CAPD, CT, NC and NA, respectively). The secretory areas were significantly narrower in NC (P < 0.05) and NA (P < 0.01) than in CAPD, and in NA than in CT (P < 0.01). The GH response to insulin did not differ in the 4 groups. The secretory area in CAPD and CT was wider after GRH than after insulin. The GH peak value of CAPD and NC was significantly higher after GRH than following insulin. No significant variation in TSH, LH and FSH was observed after the infusion of the neuropeptide, whereas PRL and F showed a reduction. The behaviour of PRL and F in NA and NC was similar after placebo and GRH.

Our data show: a) There is a greater response of GH to GRH in children than in adults; b) compared with the insulin test, GRH stimulation seems to be a reliable means of evaluating GH secretion both in normal and uraemic children owing to the absence of qualitatively different responses and to the freedom from the adverse effects or risks which follow insulin infusion; c) GRH administration does not induce any significant variation on other hypophyseal hormones and the reduction of PRL and F seems to follow the normal sleep-wake and circadian behaviour.

The uraemic syndrome is characterized by several disturbances involving all organs and systems (Tolis et al. 1980). There have been very few studies of hypophyseal function in uraemic children, particularly children on continuous ambulatory peritoneal dialysis (CAPD).

The availability of a new peptide with GH-secreting activity, first isolated from human pancreatic tumours (Guillemin et al. 1982; Rivier et al. 1982) and subsequently found in the human...
hypothesis (Ling et al. 1984), allows us to study hypothalamic responsivity to GRH in both normal and pathological conditions. This peptide selectively stimulates the secretion of GH in man (Thorner et al. 1983) and in normal children (Takano et al. 1984). Controversial effects on PRL secretion have been reported (Pintor et al. 1983; Gelato et al. 1983), but not on other anterior pituitary hormones (Borges et al. 1983; Gelato et al. 1983).

The aim of this study was to evaluate GH response to GRH in children with chronic renal failure (CRF), and to compare the results with those observed after insulin hypoglycaemia (Greenwood et al. 1966). The possibility of abnormal hypothalamic responses to hypothalamic peptides during the course of the uraemic syndrome is well-known (Chernichow et al. 1976; Hasegawa et al. 1975) so we tested the effects of GRH on LH, FSH, TSH, PRL and, indirectly through cortisol (F), on ACTH.

**Materials and Methods**

The informed consent of the patients or their parents was obtained. We studied 22 uraemic children, whose mean age was 10 years (range 2–15) and pubertal development P1-P3 according to Tanner’s score (Tanner 1962). Ten of them had been undergoing CAPD (CAPD group, CAPD) for between 3 and 24 months. The remaining 12, with a GFR of 35 ± 15 ml/min/1.73 m², were treated conservatively (Conservative Treatment group, CT).

The data obtained from uraemic patients were compared with those from 14 children with normal renal function of similar age (mean 11 years, range 5–15) and pubertal development (Normal Children group, NC). They had come to our hospital because of their short stature, but they showed normal pituitary and thyroid function. In addition we studied 13 healthy adult volunteers with a mean age of 30 years, range 25–40 (Normal Adults group, NA).

The peptide was diluted and stored as previously reported (Giusti et al. 1984) and the test was performed by iv administration of 0.01 μg/kg body weight of GRH (hp-GRF 1–40, CRB Cambridge) in 8 CAPD, 8 CT, 9 NC and 10 NA subjects. In order to save blood the number of samples was reduced: the venipuncture was carried out at 09.00 h. The following hormones were measured: GH, LH, FSH, TSH, PRL, and F.

The insulin test (0.1 U/kg body weight, iv) was carried out in 5 CAPD, 5 CT, 10 NC and 9 NA subjects on blood samples taken every 30 min for 2 h measuring GH and glycaemia.

Blood samples were immediately centrifuged and the serum stored at -20°C until the assay, which was carried out by RIA as previously described (Giusti et al. 1979, 1983): standards are calibrated for PRL against WHO Human Prolactin 81/541, 1 ng = 35 µU; for GH against WHO 66/217, 1 ng = 2 µU; for TSH against WHO 1st IRP 66/38; and for LH and FSH against 2nd IRP HMG 78/549-WHO, LH: 1 mU = 0.21 mU WHO, FSH: 1 mU = 0.74 mU WHO. Glycaemia was measured by Autoanalyzer.

Statistical analysis was carried out by means of non-parametric tests: the Mann-Whitney 'U' test to compare different groups, the Wilcoxon test to compare results within the same group, and the Spearman test to correlate data. Secretory area was determined between 0 and 120 min by the trapezoidal rule. All results were expresses as mean ± SEM.

**Results**

No adverse effects were observed after the infusion of GRH. Transient hypoglycaemia occurred in most of the patients after iv insulin administration. One CT child needed hypertonic glucose infusion during the insulin test.

**Growth hormone**

The basal plasma values of GH were similar in the 4 groups. GH administration induced a prompt response in all subjects (Fig. 1). The GH plasma levels after GRH were significantly higher in uraemic children than in normal subjects (Fig. 1), and the peak values in CAPD (P < 0.01), CT (P < 0.01) and NC (P < 0.05) higher than those in the NA group (43.5 ± 8.2, 45.0 ± 8.4, 27.8 ± 6.0 and 13.5 ± 2.6 µg/l, respectively). Peak values were reached between 30 and 90 min in the 4 groups. The secretory areas were significantly narrower in NC (P < 0.05) and NA (P < 0.01) than in CAPD, and lower in NA than in CT (P < 0.01) (Fig. 1).

Insulin administration was followed by a comparable decrease (∆%) in serum glucose in uraemic (CAPD: -50 ± 7%; CT -50 ± 5%) and in normal subjects (NC -57 ± 3%; NA -58 ± 3%).

The GH response to hypoglycaemia following insulin did not differ in the 4 groups (Fig. 1). The secretory area in CRF children was wider after GRH than after insulin (P < 0.05) (Fig. 1).
CAPD and NC, the peak value of GH after neuropeptide administration was significantly higher than that following insulin (43.5 ± 8.2 vs 13.9 ± 3.8 μg/l, P < 0.05; and 45.0 ± 8.4 vs 17.8 ± 4.2 μg/l, P < 0.05, respectively).

Other hormones
The basal plasma concentration of TSH was significantly higher in children, both normal and uraemic, than in adults (Fig. 2). Plasma LH was higher in CAPD than in CT (P < 0.05) and NC (n.s.) (Fig. 2), whereas plasma FSH levels were higher in NA than in CT (P < 0.01) (Fig. 2). Increased levels of Prl were observed in 3 children on CAPD; CAPD patients had the highest mean plasma level of Prl (Fig. 3). The basal value of F was higher in CAPD than in NC and NA (Fig. 3). After GRH infusion, no significant variation in TSH, LH or FSH was observed (Fig. 2), whereas Prl showed a reduction in CT (P < 0.05 at 60, 150, 180 min) and in NC (P < 0.05 at 120 min). F plasma levels also showed a decrease after peptide injection in CAPD (P < 0.05 at 60, 90, 120, 150 min), NC (P < 0.05 at 30, 60, 90 min) and NA (P < 0.01 at 30, 60, 90 min, P < 0.05 at 120 min).

The behaviour of F and Prl in NA and NC was similar after placebo and GRH administration (unreported data).
Fig. 2.
Percentage from basal values of LH, FSH and TSH in the 4 groups studied. Basal levels are expressed as mean ± SEM on the left of each panel. ND = NC.

Discussion

The basal values of GH, FSH and TSH have been found to be normal, whereas according to previous reports on uraemic children LH, Prl and F are increased in CAPD (Giusti et al. 1981; Ijayia et al. 1982; Perfumo et al. 1980, 1985). Both our findings and those reported in the literature (Laron et al. 1984; Pintor et al. 1983; Takano et al. 1984) show that the GH response to GRH in CAPD (Perfumo et al. 1985) and in CT is more marked than in normal children. The same has been found for adults (Thorner et al. 1983). To our knowledge there is no direct comparison between children and adults, though in a previous study on a limited number of cases (Giusti et al. 1985), we found a difference in the response of GH to GRH between the two groups. The present study confirms that observation in a larger sample.

The higher peak value and the wider secretory area of CAPD and CT compared with normal adults, and of CT compared with NC, could support the hypothesis of a greater hypophyseal store of GH, but this possibility apparently contrasts the lack of a significant difference after the insulin test.

Previous reports (Ramirez et al. 1978) have shown paradoxical response of GH to hypoglycaemia following tolbutamide. We did not find paradoxical responses, nor did we carry out metabolic studies, but in our study the per cent decrease in glycaemia was similar in the 4 groups. The comparison with insulin hypoglycaemia shows that GRH is statistically more effective in stimulating GH secretion both in uraemic and normal children. This difference could be attributed to the direct action of the neuropeptide on somatotrophic cells (Guillemin et al. 1982; Rivier et al. 1982).

The interpretation of the difference between children with CRF and control subjects is more difficult. There are data that point to the hypothalamic-hypophysis system as an explanation of the abnormal regulation of GH and TSH secretion (Ramirez et al. 1978). Recent data (Giusti et
al. 1984) show a direct inhibitory effect of dopamine on pituitary GH secretion, revealed by an increase in the responses of GH to stimulation with GRH plus domperidone as compared with GRH alone. From these data and others (Weetman et al. 1981; Bessarione et al. 1985), demonstrating an altered dopaminergic tone in patients with CRF, it would be possible to explain the higher GH response to GRH in uraemic patients.

Perhaps other mechanisms cannot be excluded.

In contrast to other neuropeptides, GRH does not induce significant effects on other hypophysial hormones in uraemic children, not with standing the presence of the characteristic increase in the basal levels of LH, F and Prl. We observed a constant and progressive decline of Prl and F plasma levels both in uraemic and controls, but the same behaviour has been detected in normal subjects after placebo administration. Prl plasma levels after GRH are mildly increased (Borges et al. 1983; Chatelain et al. 1985; Gelato et al. 1983), reduced (Pintor et al. 1983) or unmodified (Takano et al. 1984; Thorner et al. 1983). Plasma Prl variations seem to be observed more frequently in patients with isolated defects in GH or with multiple defects. The heterogeneity of these endocrinological syndromes could explain the controversial results reported (van Vliet et al. 1985). Furthermore, at least in controls, Prl seems to follow the normal sleep-wake and circadian behaviour (van Vliet et al. 1985).

In conclusion: 1) In a comprehensive series our data confirm the greater response of GH to GRH in children compared with adults; 2) compared with the insulin test, GRH seems to be a valuable means of evaluating GH secretion in uraemic children, owing to the absence of qualitatively different responses and to the freedom from the adverse effects or risks which follow insulin infusion; 3) the analysis of the response curves follow.
ing GRH and insulin leads us to hypothesize that the main difference could be in the secretory mechanism of hypophyseal cells, but further work is needed to reach conclusive results.

References


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