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PREVIOUS BETA-ADRENERGIC BLOCKADE (BAB) INCREASES GH RESPONSE TO GRF-29 IN SHORT NORMAL (SN) BUT NOT IN GH-DEFICIENT (IGH-D) CHILDREN.

Because pituitary GH release is inhibited by GIH and hypothalamic secretion of this peptide seems to be mainly dependent on β-adrenergic regulation,we have investigated if BAB could modify the pattern of GH response to GRF-29 in 5SN (3V,2F;7.8-9.6 y) and 5IGH-D (4M,1F;6.3-12.7).Blood samples for GH where collected from -15'to+ 60'according the following tests: A)Propranolol(1 mg/kg,as iv bolus at -60');B)GRF(1 mcg/kg,as iv bolus at 0');C)Propranolol(as in A)+ GRF(as in B).RESULTS($\bar{X} \pm SD$):

		-15'	0'	15'	30'	45'	60'
SN	A)	1.8±1.1	2.3±.7	4.1± 3.1*	3.5± 1.9	2.2± .9	2.3± 1.8
	B)	1.1± .6	1.1±.5	21.9±12.2*	26.2±11.6	22.5± 6.3	19.8± 9.8
	C)	1.4± .6	1.7±.5	49.7±25.3*	61.9±18☆	39.8±10☆	28.2± 5.2
IGH-D	A)	1.2± .3	1.3±.2	2.1± .9	2.5± .7	2.3± 1.1	2.2± .6
	B)	.9± .5	.9±.7	21.5± 7.8*	25.9±13.2	18.1±16	13.2± 9.1
	C)	1.3± .5	1.4±.2	32.1±19.2*	38.9±14.6	25.7±17	15.1±11.9

BAB produced a significant GH release in SN but not in IGH-D. Also,while GH response to GRF was similar in SN and IGH-D,previous BAB did increase the amplitude and latency of this response only in SN.Both facts lead us to speculate that an increased somatostatinergic tone could be the cause of short stature in some short-normal children.*p<0.02 vs 0';☆p<0.02 vs testB.

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RESULTS OF SIX MONTHS GRF TREATMENT : ANALYSIS OF GROWTH, SmC, 24^{H} GH SECRETION IN SEVEN CASES OF PARTIAL GH DEFICIENCY

7 children with growth retardation (m = - 3 ± 1 SD), with slow height velocity and partial GH deficiency in response to two pharmacological tests (maximum peak 11 ng/ml) received GRF for 6 months (10 mcg/kg/day) as a subcutaneous injection (8 p.m.). 24-hours GH secretion was studied before and after 3 months of treatment : SmC dosage and a IV GRF test (2 mcg/kg) was done before and after 6 months of treatment. Lower leg length was studied every 3 weeks by knemometry and statural growth at 3 months intervals.

Height velocity increased in 5 cases from 2.5 ± 0.5 to 4.4 ± 1.1 cm for the 6 months period and showed no change in 2 cases. Knemometric growth rate is subject to wide variations and is difficult to take into account. There was no sign of desensitization: 24-hour secretion (mx peak and I.C.) was higher after 3 months treatment (m = 16.2 ± 7.5 ng/ml and 3.7 ± 1.2 ng/ml/min before, 29 ± 17.9 ng/ml and 4.5 ± 2.9 ng/ml/min afterwards), as was the GH peak in the IV GRF test after 6 months treatment (m = 36.1 ng/ml before, 47.8 ng/ml afterwards). SmC level was higher on average after 6 months treatment (1.9 ± 1 U/ml and 0.8 ± 0.5 U/ml before treatment). The analysis of the various parameters (GH secretion, SmC) provided no elements to account for the lack of therapeutic response in the 2 cases. These results suggest that GRF treatment may be considered as a therapeutic alternative in GH deficiencies.

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TREATMENT OF GH-DEFICIENT CHILDREN WITH TWICE DAILY SUBCUTANEOUS GHRH(1-29)NH2

The biochemical and growth responses to GHRH(1-29)NH2 therapy were studied in 18 prepubertal GH-deficient children (14 idiopathic, 3 cranial irradiation, 1 septo-optic dysplasia; 16 male, 2 female, mean age 9.5 years, range 6.8 - 14.2 years). GH deficiency was defined as a peak GH to stimulation of less than 7 mU/l. Fourteen children had received hGH treatment which was stopped at least 3 months before the trial. GHRH was given as twice daily sc injections in individual doses of 250 µg (children less than 20 kg bw), and 500 µg (greater than 20 kg). Peak serum GH response to GHRH before treatment was 25.8 + 6.3 mU/l (mean + SE) and after 3 months 27.4 + 4.2 mU/l; indicating no desensitisation effect. Thirteen of the 18 showed an increment in height velocity after 3 months therapy, in 6 this was greater than 2 cm/year and in 3 greater than 5 cm/year. Three children showed a greater height velocity on GHRH than on hGH. Eight children have completed 6 months therapy and 3 have shown an increment in height velocity of 0.4, 2.5, and 3.1 cm/year. There was no correlation between the growth response at 3 months and pre-treatment GH response to GHRH. In conclusion, we have shown that twice daily sc GHRH therapy is a safe treatment which promoted linear growth at 3 months in 13 of 18 GH-deficient children. However, predictors of good growth responses could not be identified.

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EFFECTS OF GROWTH-HORMONE - RELEASING HORMONE (GRF) IN 5 CHILDREN WITH IMPAIRED GROWTH HORMONE (GH) SECRETION.

5 children (8.24+/-3.63 years) with growth retardation (3.4 +/-0.9 DS)bone age retardation (3.13+/-2.40 years) and insufficient growth velocity (3.9+/-0.6 cm/year) related with complete (n=2) or partial (n=3) GH deficiency were treated with a daily dose of 300 mcg GRF administred subcutaneously (SC)every other week for a 6 months period. GH response to SC GRF administration, GH and GRF antibodies and somatomedins were studied on repeated blood samples performed on day 1 and day 8 of the first week of treatment as well as at the end of the 6 months therapy. Growth velocity increased to 6.16+/-1.17 cm/year. 3 of the 5 patients have accelerated growth mainly for the first 3 months. Linear growth was increased in complete (+2.5 and 4.3 cm/year) more than in partial (+0.4, +0.8 and +3.3 cm/year) GH deficient children. The area under the GH curve after GRF administration was 1050.7+/-767.7 on day 1, 472.1+/-103.2 on day 8 and 631.9 +/-148.1 ng/ml x min. after 6 months therapy. No major change in other hormonal evaluations was noted.
These results confirm that GRF can stimulate linear growth in some GH deficient children and lead to discuss the role of limiting factors in its long term effects such as desensitization, antibodies or somatostatin.

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PULSATILE GROWTH HORMONE RELEASING HORMONE TREATMENT OF GH DEFICIENCY

We have treated 11 prepubertal children (7M;4F) with idiopathic GH deficiency due to pituitary hypoplasia using GHRH 1-40. This was administered subcutaneously for 4 pulses at 3 hourly intervals at night in a dose of 1-2µg/kg/pulse. Blood samples for GH concentrations were taken at 20 minute intervals for 24 hours before treatment and throughout the study monthly at night.

Pulsatile GH secretion was induced in 10 children from the first night of treatment and the response augmented with time. Growth velocity in 8 of 11 children increased from 3.3cm/yr (range 1.7 to 4.9) before treatment to 6.9cm/yr (range 5-8.5) on GHRH. 2 children had no change in height velocity and one had a progressive diminution of GH secretion and a fall in growth velocity.

GHRH (1µg/kg) was also administered intravenously to all children before treatment and at 3 monthly intervals. Although a GH response was seen on all occasions, the responses predicted neither the GH concentrations nor the growth velocities obtained on long term s.c. treatment.

Pulsatile administration of GHRH 1-40 was effective in inducing GH secretion and promoting growth acceleration in the majority of children with idiopathic GH deficiency.

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A SIMPLIFIED METHOD FOR SMALL SCALE PURIFICATION OF INSULIN-LIKE GROWTH FACTOR I / SOMATOMEDIN C (IGF I/ SM C) FROM COHN FRACTION IV

Starting from Cohn fraction IV of human plasma we earlier described a multiple step procedure which resulted in ug amount of IGF I/SmC of relative high purity (2oo µU/µg)+.
In the meanwhile we have further modified this method: 2o grs. of acetone dried Cohn fraction IV are suspended in 1% NaCl/formic acid, pH 3.o. After precipitation of the IGF I containing proteins in the supernatant by addition of 5 M NaCl the precipitate is resuspended in 2 N acetic acid (AA) /ethanol (1:4). Denatured proteins are discarded by centrifugation, and after evaporation the supernatant is chromatographed on Sephadex G 5o in 1 N AA. IGF I containing fractions (approx. 12 µg IGF I, purity of approx. 9o%) are purified by Immobiline^{R} isoelectric focusing (IEF) (pH 8-1o). The IGF I band, focusing at pH 8.3 finally is purified using a HPLC reversed phase C-18 column in a 25-65% acetonitrile gradient cont. o.o5% TFA. IGF I elutes in a single peak at approx. 4o% acetonitrile. Since the G 5o material contains no IGF II as demonstrated in preparative Immobiline^{R} IEF pH 4-1o gradient, even this material can be applied for antibody production. The final step material of highest purity is suitable for biological studies and in vitro investigation of IGF I receptor interactions on human lymphocytes and fibroblasts.

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