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95 ALTERED SEXUAL MATURATION IN MALE RATS PASSIVELY IMMUNIZED AGAINST rGRF FROM 15 TO 40 DAYS OF LIFE

GH deprivation following passive immunization (PI) against rGRF markedly affects somatic growth in rats. Since it has been postulated that GH and probably IGF-I have a permissive role on sexual maturation, the effect of GH deprivation on the course of sexual maturation was tested. Male rats were treated with a potent anti-rGRF serum between 15 and 40 days of life (d). Body weight (BW) of treated rats averaged 76.3% of that of control rats at 40 d and was maximally affected at 50 d (56.9%) after which age, treated rats started to grow normally. At 40 and 50 d, plasma GH was undetectable and plasma IGF-I levels averaged 30% of those of control rats. At 70 d, GH & IGF-I secretions were normal. At 40 d, testes and seminal vesicles of treated rats were small-for-age in agreement with significantly decreased plasma levels of testosterone and FSH. At 50 d, despite maximum delay of somatic growth, progress of sexual maturation was found to be almost normal. At 40 and 50 d, pituitary weight and contents of GH, FSH, and LH were severely decreased but became normal at 70 d. In conclusion, GH deprivation markedly affected somatic growth and induced a transient delay of sexual maturation secondary to a partial inhibition of synthesis and release of LH & FSH. This inhibition of LH & FSH secretion may result from central inhibition of GnRH secretion or from impaired development of the pituitary gland.

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96 TREATMENT OF GROWTH HORMONE DEFICIENT CHILDREN WITH SOMATOCRININE

The availability for clinical use of somatocrinine growth hormone releasing hormone (GRF) brings about the possibility of treatment of growth hormone deficient children (GHD) of hypothalamic origin. We present the results of the first 6 months of treatment of GRF in 20 GHD children. Ten boys and 10 girls with mean chronological age of 10.7 ±2.7 yr, bone age 6.1 ± 2.5 ,,yr'' and with a mean growth retardation of 4.7 ± 0.6 SD were treated with GRF 1 - 44 SANOFI by daily (N = 11) or thrice weekly (N = 9) subcutaneous injection in doses of 10 ug/kg body weight. All of the children were in prepubertal stage and in all the peak GH response to clonidine and l'dopa provocative tests was below 5 ng/ml. Nine patients had TSH deficiency and were parallely treated with l'thyroxine. The GRF i.v. bolus test was performed before treatment and 2 and 6 months after initiation of treatment. In 9 out of 20 patients acceleration of growth velocity was found. Three patients reached a growth velocity of more than 4.4 cm per yr. Growth velocity during the treatment was significantly correlated with peak GH response to GRF i.v. bolus before (r= 0.6786) and during the treatment (r= 0.4863 and r = 0.5947, respectively). The growth velocity was greater in younger children and in those with less advanced bone age. Acute response to GRF was significantly greater after 6 months of treatment than before the treatment (mean peak GH response 2.9 ± 3.0 and 7.6 ± 8.1ng/ml respectively, $p < 0.05$). No side effects of the treatment were observed and immunological tolerance was good. We concluded that chronic administration of GRF is well tolerated and resulted in enhanced growth in some of the GHD children and evoked better response of somatotrophs to GRF i.v. bolus. The GH response to a single i.v. GRF bolus may have a prognostic value for growth response to GRF therapy.

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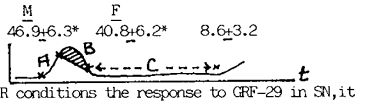
97 HYPOTHALAMIC-SOMATOTROPH RHYTHM (HSR) AND GH RESPONSE TO GRF-29 IN SHORT NORMAL (SN) AND GH-DEFICIENT CHILDREN (GH-D).

In a previous work we demonstrated that in adults timing of GRH stimulation in relation to the pattern of spontaneous GH secretion could condition GH response. To investigate if there was a similar situation in children, a GRH test (GRF-29, Serono 1 mcg/kg, iv bolus) was performed in 17 SN (8M, 9F, 7-11 y) and 6 GHD (3M, 3F, 8-12 y) at 09.30 h after an overnight fast and 30' resting. From the analysis of plasma GH variations (-30', 0') prior to stimulation, 3 theoretical phases in HSR were established: A) Secretion Phase; B) Secretion Plateau; C) Refractory Phase, (see fig.). GH peak after GRF-29 was evaluated according to the theoretical phase at testing. RESULTS (x±SEM).- A very high correlation (Spearman's test) was obtained between pre-GRF GH increments (+,- or 0) and GH peak in SN ($r=0.81$, $p<0.0001$). No differences were found in the distribution per phase between M and F SN. (GH=ng/mL).

	nº per phase		GH peak	GH peak by sex		GH peak GHD
PHASE	M	F		M	F	
A	6	5	43±5.3 *	46.9±6.3*	40.8±6.2*	8.6±3.2
B	1	2	14.5±1			
C	1	2	6±3			



While it is clear that endogenous HSR conditions the response to GRF-29 in SN, it appears that sexual HSR dimorphism, previously reported by us, must begin after puberty, because both the sexual distribution per phase and GH peak were very similar. The fact that SN in phase C showed similar responses to those in GHD indicates that the functional status of HSR must be taken into account to minimize errors in diagnosis after GRH test and possibly also in GRH therapy.

*$p<0.005$ vs. B and C. Partially supported by FISS 87/1359

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98 CHILDREN WITH IDIOPATHIC SHORT STATURE SHOW A GREATER RESPONSE TO GHRH THAN INSULIN HYPOGLYCAEMIA; RESPONSE TO GHRH (1-29)NH2 IN 16 NORMAL SUBJECTS AND 55 CHILDREN WITH SHORT STATURE.

Growth hormone-releasing hormone (GHRH) given as an iv bolus is an effective test of readily-releasable pituitary GH. In young adults the GH response to GHRH and the insulin tolerence test (ITT) are comparable. We have studied the response to 100ug iv of GHRH (1-29)NH2 in 16 normal male subjects (aged 19-36 yrs), 21 children with idiopathic short stature (ISS, peak GH during ITT 20-81 mU/l), 8 with borderline GH deficiency (GH 10-20 mU/l), and 34 with GH deficiency (GH <10 mU/l; 18 patients with idiopathic GH deficiency, 5 with structural lesions, 3 with optic nerve hypoplasia, and 8 post-irradiation GH deficiency. The mean (range) peak GH after GHRH was 62(12-220) mU/l in normal subjects, in patients with ISS 72(13-195), borderline GH deficiency 55(23-102), idiopathic GH-deficiency 31(<1-104), structural lesions 14(3-45), optic nerve hypoplasia 26(4-47), and post-irradiation 19(9-35) mU/l. The pattern of response was identical in all groups (peak GH 15-75 mins) although GH-deficient patients had significantly lower GH responses than the normal subjects. All patient groups showed a significantly greater GH response after GHRH than hypoglycaemia. In particular, in ISS the GH response to GHRH was identical to that of normal subjects and significantly greater than their response to the ITT ($p=0.011$). The discrepant response to GHRH and the ITT suggests a suprapituitary cause for the decreased GH secretion and suggests that children with ISS as well as GH deficiency may respond to treatment with GHRH.

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99 CONTINUOUS S.C. INFUSIONS OF GHRH ANALOGUE GHRH(1-29) DO NOT DESENSITIZE THE SOMATOTROPH.

We have shown that GHRH administered subcutaneously in a pulsatile fashion is effective in the treatment of GH deficieny. We have studied the effect of continuous 8 day s.c. infusions of GHRH(1-29) on GH secretion in 10 normal adult male volunteers aged 19-24 years.

24 hour GH profiles were performed on day 0 and on days 1 and 8 of the infusion. Doses of GHRH were doubled progressively from 7.5 to 120ng/kg/min. Baseline profiles were within normal range for our laboratory.

GH secretion was not augmented by doses of 7.5 and 15ng/kg/min. With 30ng/kg/min significant increases in GH pulse frequency and amplitude were achieved with normal profiles. Doses of 60 and 120ng/kg/min induced high pulse frequency (up to 13 pulses/24 h) and we know from clinical studies that GH neurosecretory dysfunction (>9 pulses/24 h) fails to produce adequate growth. 120ng/kg/min also produced very high GH peaks (max 122mU/L) which failed to return to the baseline between pulses, an abnormal pulse profile.

There has been no evidence of desensitization of the hypothalamo-pituitary axis at any dose over one week. The profiles indicate that a promising therapeutic regimen might be achieved by the continuous administration of GHRH1-29.

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100 GH RESPONSE TO GRF IN HYPOTHYROID CHILDREN.

Primary hypothyroidism has been reported to be associated with blunted GH responses to different stimuli which reverse to normal under thyroid hormone replacement. Whether such a pattern reflects an alteration in hypothalamic or pituitary mechanisms is unknown. In the present study we investigated GH response to i.v. (1 µg/Kg) GRF (1-29, Serono) in 7 untreated hypothyroid children (mean ± SD T4 4.0 ±1.4 µg/dl, T_3 39.4 ± 10.6 ng/dl, TSH 113 ± 74 µUI/ml) and in the same L-T_4 substituted 7 patients (T_4 15.0 ± 4.8, T_3 165.3 ± 19.7, TSH 7.0 ± 0.5), who served as controls. Either baseline (8.1 ± 6.0 vs 3.9 ± 4.0 ng/ml) or GRF stimulated GH serum levels at 5 to 120 min did not significantly differ in the hypothyroid children than in the controls. Both GH max peak (51.5 ± 45.2 vs 28.5 ± 28.6; 2 $p > 0.1$) and GH Δ after GRF (43.4 ± 42.3 vs 25.0 ± 27.2; 2 $p > 0.2$) were only slightly but not significantly higher in the hypothyroids. No relationship was found between either GH peak or GH Δ and thyroid function tests in both groups. Our data indicate that that somatotroph sensivity to GRF and pituitary GH reserve as well are not substantially impaired in hypothyroid subjects. The subnormal GH secretion associated with thyroid failure, therefore, may probably reflect a hypothalamic disorder. Such conclusion contrasts with that of a recent study in hypothyroid rats (Dieguez et al, J Endocr 109,53,1986).