45 SmC RESPONSE TO hGH AND GH-RF IN GH-RF-DEFICIENT CHILDREN

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4 GH-RF deficient children (1 with isolated GH-deficiency, 2 with GH-TSH deficiencies, 1 with GH-TSH-ACTH-deficiencies) were administered s.c. hGH (after the previous hGH treatment had been discontinued 1 week before the study) at a dose of 0,1 UI/Kg, according to usual substitutive therapy, at times 0 and 48 h. After a further week without therapy the subjects were administered i.v. GH-RF at a dose of 3 µg/Kg at times 0,8,16,24,32,40,48,56,64 h. SmC blood samples were collected at time 0 and, after hGH and GH-RF administrations, at times 4,8,12,16,24,28,32,36,40,48,52,56,60,64,72 h. In all patients a significant GH-response ($\searrow$ 4 ng/ml) was attained after each GH-RF administration. In 3 subjects a SmC increase was observed after both hGH and GH-RF administrations. In 1 case there were no changes in SmC levels after both hGH and GH-RF administrations. By calculating the integrated areas of the SmC curve, the values obtained after hGH and GH-RF administrations were higher in 2 cases after the GH-RF injection, higher in 1 case after the hGH injection, and in 1 case the areas were similar. In our patients and in our experimental conditions we did not find differences in the SmC release between the usual hGH therapy and GH-RF administration.

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USE OF GRF(1-29) FOR GROWTH HORMONE STIMULATION.

Eleven healthy volunteers (20-30 yrs.) were given 1 µg/kg BW as an i.v. bolus of both GRF(1-40) and GRF(1-29) (KabiVitrum AB/ Sweden). Conditions were standardized and blood was sampled at -15, 0, 15, 30, 45, 60, 90, and 120 min. After GRF(1-29) flush was observed in 10 cases, while after GRF(1-40) in two cases. No other side reactions were noted. Maximal GH increments above basal levels were not different (GRF(1-29): $\tilde{x}$=36.7 ng/ml (range: 9.0-114.1 ng/ml); GRF(1-40): $\tilde{x}$=31.1 ng/ml (range: 8.3-98.2 ng/ml)), but were significantly correlated (r=0.71; p<0.01). In both tests GH peaked between 15 and 45 min. - So far 51 children were tested in an identical mode. In the 32 cases classified as non-GH deficient all GH levels rose to more than 8 ng/ml (1. IRP) above basal with trends according to sex and age. In 19 cases GHD had been established by testing with insulin and arginine, and Sm measurements. In these patients GH increments were: <3 ng/ml in 10, 3-5 ng/ml in 6, and >9 ng/ml (14.6, 9.1, 35.8) in 3 cases. Thus, GRF(1-29) is suitable for GH testing. Easier synthesis makes it also appear to be a favourable alternative for attempts to treat hypothalamic growth hormone deficiency.

47 EFFECT OF CHRONIC GRF ADMINISTRATION ON MALE RATS DURING PUBERTAL DEVELOPMENT

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The long term effect of daily injections of GRF(1µg/kg bw,sc) was studied in developing male rats. In two additional groups GRF was stopped on day 30 and on day 50. Weight and length were measured at 5 days intervals, GH and somatomedin were measured at diverse time points by RIA. When compared to the controls, GRF treated animals did not differ in length at the end of the observation period (day 75). On the other hand, the growth pattern was markedly different. GRF treated animals grew faster from day 15 to day 25, and had significantly lower GH levels than the controls on day 30 (3.0±1 vs 23.0±12 ng/ml, p<0.01). Growth velocity in the GRF group decreased slightly until day 45, on which experimental and control group did not differ any more in length. On the contrary, a significant catch up in length (p<0.001), followed by a decrease in growth velocity was observed when GRF was stopped on day 30, final length not differing from the controls. This pattern was not observed when treatment was stopped on day 50. On the other hand, a significant and lasting increase in weight was observed after GRF withdrawal in both groups. These animals were on day 75 significantly heavier than the chronically treated and the controls (286±16 and 287±8 vs 272±7 and 264±12 gr, p<0.05). The results indicate that chronic GRF administration might alter GH secretion possibly by down regulation of pituitary receptors, and affects the pubertal growth pattern, but not the final length.

48 THE EFFECT OF WEANING AND MATERNAL SEPARATION UPON GROWTH HORMONE RESPONSE TO GROWTH HORMONE RELEASING FACTOR IN THE INFANT RHESUS MONKEY.

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Human infants with the maternal deprivation syndrome have poor growth and elevated plasma growth hormone (GH) concentrations which have been ascribed to either psychological factors or inadequate caloric intake. Infant Rhesus monkeys were studied as a potential model of the psychological or nutritional effects of weaning and maternal separation upon the GH response to growth hormone releasing factor (GHRF). After 60 min of equilibration, six 3-month old monkeys at the California Primate Research Center were given 10 mcg/kg of GHRF intravenously and sera was analyzed for GH by radioimmunoassay at -30,-15,0,7,15,30,60 and 120 min. The infants were then weaned from their mothers and housed in nursery observation cages and 7 days later the GHRF study was repeated. Two animals had no change in peak GH values after weaning, while the other four had a significant increase in peak GH and rise in GH after GHRF (mean ± SD).

	Basal GH		Peak GH		Delta GH	
weaning:	pre	post	pre	post	pre	post
	4.1±1.5	5.4±1.9	7.1±0.84	24.5±6.6	3.0±2.2	19.1±5.5
	non-significant		p<.001		p<.001	

The changes were unrelated to nutritional deprivation as all animals were eating normally and gaining weight by the second study. The weanling Rhesus monkey may reflect the early endocrine changes of maternal deprivation in children.

49 INSULIN-LIKE GROWTH FACTOR(IGF)AND CARRIER PROTEIN SERUM LEVELS IN TALL GIRLS ON HIGH-DOSE ESTROGENS.

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To further elucidate the behavior of IGF under high-dose estrogens we have determined total IGF (tIGF) by a competitive protein binding assay, IGF-I by RIA and IGF carrier protein levels by a modification of the protein binding assay in 17 excessively tall girls (mean age ± SD:13.9 ± 1.3 yrs, mean bone age ± SD:12.4 ±0.6 yrs) before and 12 months after initiation of estrogen treatment (ethinylestradiol(EE) 300 µg per day). Before therapy the mean ± SD serum level of tIGF was 427 ± 43.4 µU/ml, of IGF-I 182.9 ±36.4 ng/ml. tIGF decreased to 370.7 ± 72 µU/ml (86% of level before), IGF-I to 128.3 ± 19.3 ng/ml (70% of level before). Carrier protein concentrations did not change significantly (430.3 ±58.4 ngeq/ml vs. 415.9 ± 77.5 ngeq/ml, n.s.) There was a significant positive correlation between IGF-I and growth rate (r=0.55, p<0.05) and a significant negative correlation between ΔIGF-I and growth rate (r=0.66, p<0.001) on EE.- Our results are in keeping with the assumption that growth inhibition observed with high-dose estrogens is at least in part due to a specific effect on IGF production. While the net carrier protein content is unchanged, the possibility has to be tested that IGF metabolism may be increased by a change of the carrier protein composition.

50 BODY SIZE AND GROWTH VELOCITY PARALLEL INSULIN-LIKE GROWTH FACTOR (IGF) I LEVELS IN CHILDREN AND ADOLESCENTS WITH CONSTITUTIONAL VARIANT STATURES.

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In subjects with various growth rates (without any clinical or biological abnormalities) IGF I related peptides increase with age in a similar way but at different levels. In comparison with normal subjects (height = mean for age ± 1 SD), IGF levels measured by competitive protein-binding assay were found significantly higher in subjects with tall stature (height > mean for age + 2 SD) and significantly lower in subjects with short stature (height < mean for age - 2 SD). Analysis of the data altogether shows that 1) the positive correlation between IGF and height (r = 0.71, p < 0.001, n = 227) does exist without respect to age, as shown when studying the ratios of height/normal height for age vs IGF/normal IGF for age (r = 0.61, p < 0.001); 2) in subjects whose growth was followed up (tall and short stature) a positive correlation is found between the ratios of growth velocity (gv)/normal gv for age and IGF/normal IGF for age (r = 0.52, p < 0.001, n = 111). The differences in IGF levels between the three groups of subjects (which contrast with no differences in GH levels in the usual pharmacological tests) disappear after epiphyseal fusion. These results suggest that, during growth, individual differences in height and growth velocity seem to be directly related to the IGF secretory capacity. This provides further evidence for an important rôle of IGF I in the physiological control of growth.