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EVIDENCE FOR PARTIAL GROWTH HORMONE (GH) INSENSITIVITY AMONG "IDIOPATHIC" SHORT STATURE (ISS) PATIENTS TREATED WITH GROWTH HORMONE. K.M. Attie, L.M.S. Carlsson, A.C. Rundle, and the National Cooperative Growth Study (NCGS). Genentech, Inc., South San Francisco, CA and University of Göteborg, Sweden.

Data from the NCGS shows that some patients with ISS (defined as a max. GH >10 ng/mL) have abnormally low GH-binding protein (GHBP) levels. Since low circulating levels of functional GHBP are found in patients with GH insensitivity syndrome, it is possible that these patients have partial GH insensitivity. There were 511 ISS patients in NCGS with GHBP measurements performed at baseline. Of these, 101 (20%) had GHBP SD scores ≤-2 compared to sex- and age-matched normal children. The table compares this group with the "normal-GHBP" group [mean ± SD (n)]:

Baseline characteristics:	GHBP SD ≤ -2	GHBP SD > -2	p-value
Age (yr)	10.5±3.1 (101)	11.4±2.8 (410)	0.0028
Body mass index	15.7±1.6 (100)	16.6±2.2 (409)	0.0007
Height SD score	-2.9±0.7 (101)	-2.9±0.6 (410)	0.81
IGF-I (ng/mL)	99.9±61.4 (101)	149.4±101.3 (410)	0.0001
Mn. 12h GH (MAb, ng/mL)	2.8±1.1 (100)	2.3±1.1 (407)	0.0001
Pre-Rx growth rate (cm/yr)	4.0±1.9 (76)	4.4±3.7 (286)	0.70
1st yr growth rate (cm/yr)	8.1±1.6 (60)	8.4±1.9 (256)	0.29

There was a significant ($p \leq 0.0001$) linear correlation of GHBP SD score with IGF-I concentration ($r=+0.28$) and mean 12h GH concentration ($r=-0.17$). CONCLUSIONS: ISS patients with low GHBP levels, compared with those with normal GHBP levels, had lower IGF-I levels and higher mean 12h GH levels, suggesting partial GH insensitivity; however, the two groups had similar height SD scores and first year response to GH therapy.

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POOLED 24 HOUR AND DIURNAL LH VALUES: STUDIES IN CONTROL AND IRRADIATED CHILDREN.

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Using a sensitive DELPHIA (time-resolved fluoroimmunoassay) for measurement of LH, we have reanalyzed 250 spontaneous secretory studies. Samples were obtained every 20 minutes and aliquots from timed intervals were pooled: 24HR = 0800-0800h, AM = 0800-1600h, PM = 2200-0600h. Pools were assayed for LH (sensitivity 0.0365 IU/L); and FSH, GH, testosterone (T), and estradiol (E_2) were measured by radioimmunoassay. In 89 control males, there was a rise in 24HR LH at pubertal stage (PS) II (3.47±3.97) over PS I (0.55±0.69, $p<0.001$), with a decrease again in PS III (1.46±0.38). This pattern was not seen in the 51 control females. In the 85 pubertal controls, there was a diurnal variation with PM LH (3.92±3.78) higher than AM LH (1.79±1.65, $p<0.01$). There was a weak correlation of 24HR LH with 24HR GH ($r=0.24$, $p<0.02$) and stronger correlations with 24HR FSH ($r=0.56$), 24HR E_2 ($r=0.37$), and 24HR T ($r=0.35$). Interestingly, cranially irradiated PS I children (n = 12) had higher 24HR LH (3.32±6.00) compared to 66 PS I controls (0.62±0.85, $p<0.001$) and FSH (13.25±18.02 vs 2.03±1.78, $p<0.001$), whereas their mean T and E_2 where not different. Pooled LH values are useful additions to spontanous secretion studies and give information on pubertal changes, diurnal variation, and early puberty in cranial irradiation.

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ANALYSIS OF GROWTH HORMONE SECRETORY DEFICIENCY IN RODENT MODELS

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Growth hormone (GH) secretory responses to provocative stimulation tests are often blunted in short statured children. The objective of the present study was to evaluate various pituitary factors that may contribute to low GH secretion using rodent models that are hyporesponsive to GH secretagogues. Plasma GH concentrations did not increase above basal values (1.7 ± 0.7 vs 316 ± 89.9 ng/ml) after GHRH and/or GHRP administration in mice lacking pituitary receptors for GH. Plasma GH increased in dwarf rats with defective cAMP second messenger systems; however, concentrations were lower than normal (67 ± 3 ng/ml vs 1396 ± 76 ng/ml; $p < 0.001$). Stimulated GH secretion in old rats administered GHRH or GHRP was significantly lower than in young rats (393 ± 69 ng/ml vs 1477 ± 111 ng/ml; $p < 0.01$), whereas plasma GH concentrations were comparable in both age groups administered GHRH and GHRP (1079 ± 106 ng/ml vs 1159 ± 93 ng/ml). Chronic co-administration of GHRH and GHRP to old rats also restored youthful patterns of GH secretion, increased pituitary GH concentrations (7 ± 2 µg/mg vs 51 ± 9 µg/mg; $p < 0.001$) and increased serum IGF-1 (413 ± 77 ng/ml vs 810 ± 82 ng/ml). These data suggest that blunted responses to provocative GH releasing stimuli result from defects in pituitary receptors, second messengers and/or to inadequate pituitary stimulation; each with different effects on GH secretion. Receptor defects completely blocked and second messenger defects partially blocked GH secretory stimuli, whereas inadequately stimulated pituitaries gave differential responses to GH releasing peptides. Thus, by comparing responses to lone and paired GH secretagogues it may be possible to discern the etiology of GH secretory deficits in certain short statured children. When GH secretory deficiency results from inadequate pituitary stimulation, co-administration of GH secretagogues may restore proper GH secretion as well as increase pituitary GH stores and serum IGF-1 concentrations.

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THE VARIABILITY OF OXANDROLONE LEVELS IN SERUM AND URINE POSES NEW QUESTIONS TO ITS USE FOR TREATMENT OF CDGA. H.A.WOLLMANN, W.SCHÄNZER*, M.DONIKE* and M.B.RANKE

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Low dose (0.05 mg/kg day) Oxandrolone (OX) treatment in prepubertal children [n=13; CA 9.8y (4.7-11.2); HTSDS -2.5 ± 0.5] with CDGA increased HV from 5.0 ± 1.1 cm/yr to 7.1 ± 0.8 cm/yr after 6 months and 8.6 ± 1.4 cm/yr after 12 months of therapy. In some children however, rapid bone maturation compromised growth prognosis. Concentrations of OX (serum), epi-OX and other physiological steroid metabolites (serum, urine) were measured by gas-chromatography/mass-spectrometry in these children before and on OX. Within 24 h after OX, levels in serum varied between 8.7 and 0.4 ng/ml. Excretion of OX [epi-OX] in urine varied between 16 and 223 µg/24h (x = 64.1 ± 69 µg/24h) [3.4 and 12.8 µg/24h (x = 5.9 ± 3.6 µg/24h)] . OX treatment suppressed androgen excretion [Androsteron from 536 ± 498 before to 370 ± 192 µg/24h on OX; Etiocholanolon from 357 ± 349 to 169 ± 92 µg/24h]. This effect was more pronounced in children with primarily higher androgen excretion.

Conclusion : OX is widely used, but knowledge of its action and metabolism is scarce. Individual differences in metabolism and excretion may be responsible for the side effects, e.g. rapid bone maturation. The influence of OX on the metabolism of endogenous androgens indicates an androgenic action of the substance. Individual dose adjustment appears to be necessary.

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RADIOIMMUNOLOGIC DETERMINATION OF GHBP IN SERA OF CHILDREN WITH SHORT STATURE. J. Kratzsch*[1], W.F. Blum[2], T. Selisko*[1] and E. Keller[1], Dept. Clinical Chemistry and Pediatrics, Universities of [1]Leipzig and [2]Tübingen, Germany

No assays have been reported so far for quantitative immunologic measurements of GHBP-related peptides in human serum. For this purpose polyclonal antisera were raised in rabbits against partial sequences of the extracellular domain of the human GH receptor, which were selected on the basis of secondary structure calculations suggesting their location on the surface of the molecule together with high flexibility. One of the peptides was finally chosen for establishing a RIA using this pentadecapeptide for radiolabelling and for preparation of standards. The specificity of the antiserum was examined by FPLC size exclusion chromatography (SEC) and Western blotting (WB). In SEC, GHBP RIA activity coeluted with the GH-binding activity at 55 kDa with a minor peak at 106 kDa. By WB, 2 bands at 54 and 73 kDa were visible. High concentrations of GH did not interfere in the GHBP RIA. Results of GHBP measurements were referred to the peptide standard and are given as ng/ml peptide equivalents. **Results**: Short children with low IGF-I levels (<5th percentile, n=13, age 11.0±2.3 yr) had significantly decreased GHBP levels as compared to short children with normal IGF-I levels (n=13, 12.2±2.3 yr) or an age-matched control group (n=26, 11.6±3.6 yr): (mean±SD) 31±15 ng/ml versus 48±13 ng/ml or 46±23 ng/ml resp. ($p<0.05$). Patients with chronic renal failure (CRF) with residual glomerular filtration (n=10, age 11.1±3.8 yr) had markedly diminished GHBP levels (11±4 ng/ml, $p<0.001$), whereas patients with end-stage renal failure (ESRF; n=10, 13.0±2.9 yr) showed a remarkable interindividual variation (37±35 ng/ml, range 4 - 101 ng/ml). **Conclusions**: 1) The results of RIA measurements compare qualitatively well with functional assays. 2) Low IGF-I levels in short children may be related to low GHBP (or GH receptor) levels. 3) Low GHBP levels in uremic patients may be due to impaired synthesis. 4) In extreme cases of ESRF diminished GHBP synthesis may be counterbalanced by impaired clearance leading to elevated GHBP levels.

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THE SHORT-TERM INCREASES OF IGF-I AND IGFBP-3 DURING GH TREATMENT PREDICT THE LONG-TERM GROWTH RESPONSE IN SHORT CHILDREN. W.F. Blum[1], S. Rosberg[2], M.B. Ranke[1] and K. Albertsson-Wikland[2], [1]University Children's Hospital, Tübingen, Germany, and [2]Int.Ped.Growth Research Centre, Dept.of Pediatrics, University of Göteborg, Sweden

The treatment of short children without GH deficiency (GHD) poses a major question: whether or not short-term changes of GH-dependent parameters could predict the long-term growth response to GH treatment. For this purpose, serum IGF-I and IGFBP-3 levels were studied in short prepubertal children without "classical" GHD as defined by a peak GH level above 20 mU/L in the arginine-insulin-tolerance test (5 girls, 33 boys, age 8.9±1.9 yr) receiving 0.1 IU rhGH per kg body weight daily. Height velocity (HV) was determined during a 1-yr pretreatment period and during the 1st (n=38) and 2nd (n=32) year of treatment. IGF-I and IGFBP-3 were measured by specific RIAs at start of therapy (index 0) and after 1 month (index 1m). **Results**: HV (mean±SD) increased from 4.97±1.04 cm/yr to 7.60±0.99 and 6.42±1.24 cm/yr during the 1st and 2nd year resp. The 1 month increase of IGF-I levels was from 131±54 µg/l to 199±90 µg/l and of IGFBP-3 from 2.84±0.68 mg/l to 3.57±0.90 mg/l. The correlation coefficients and p-values between IGF-parameters ($IGF-I_0$, $\Delta IGF-I = IGF-I_{1m} - IGF-I_0$, $\%IGF-I = IGF-I_{1m}/IGF-I_0$, IGFBP-3 accordingly) and the increases of HV during the 1st (ΔHV_1) and 2nd year (ΔHV_2) are given below ($r_s(p)$):

	$IGF-I_0$	$\Delta IGF-I$	$\%IGF-I$	$IGFBP-3_0$	$\Delta IGFBP-3$	$\%IGFBP-3$
ΔHV_1	-.33(.0410)	.13(.1650)	.33(.0415)	-.44(.0057)	.33(.0442)	.43(.0066)
ΔHV_2	-.05(.7738)	.38(.0358)	.43(.0177)	-.02(.9348)	.62(.0002)	.54(.0020)

Conclusions: 1) Low basal IGF-I and IGFBP-3 levels predict a good growth response during the 1st year, but not thereafter. 2) The predictive potential of the short-term increases of IGF-I and IGFBP-3 is better for the 2nd year than the 1st year. 3) IGFBP-3 is superior to IGF-I due to its negligible circadian fluctuations during GH therapy.