326

BODY COMPOSITION CHANGES DURING AND AFTER GROWTH HORMONE (GH) THERAPY FOR SHORT STATURE. G.D Ogle, P.W. Lu, B. Moore, R. Howman-Giles*, J. Briody*, C.T. Cowell. Robert Vines Growth Research Centre & *Department of Nuclear Medicine, Royal Alexandra Hospital for Children, Sydney, 2050, Australia.

GH deficiency (GHD) results in accumulation of body fat (BF) and decreased lean body mass (LBM). We assessed these parameters during the first 12 months (mo) of GH Rx in 78 short children (mean age 10.7±3.0 yr; 19 with GHD, 48 "short slowly growing" (SSG), and 11 with Turner syndrome (TS)), and during the first 6 mo after discontinuation in 11 adolescents (age mean±sd 15.9±1.3 yr; 5 GHD, 3 SSG, 3 TS). Body composition was assessed at 6 month intervals by Dual Energy X-ray absorptiometry (DEXA, LUNAR Corp.), and also by four-site skinfold (SF) measurement. The agreement on %BF by DEXA and SF techniques on 270 children at 410 occasions was high (r²=0.81).

Before Rx, %BF was highest in TS. DEXA %BF with Rx fell at 6 mo (p<0.005, <0.01, <0.2 respectively for each group; response in GHD > SSG & TS (p<0.001)), and remained lower than baseline at 12 mo (see Figure). SF %BF results were similar. Mean fat mass (FM, in kg) declined in all groups at 6 mo (sig. in GHD and SSG). LBM increased by a mean of approximately 2kg/6 mo in all groups (<0.001). Android/gynoid fat ratio (by DEXA, trunk fat/leg fat) increased in the SSG group from 0.64±0.22 to 0.70±0.19 at 6 mo (p<0.01) and 0.76±0.27 at 12 mo (p<0.002), and declined (not sig.) in GHD. In the 11 adolescents ceasing GH, % BF rose from 28.9±14.3 to 32.9±13.6% (p<0.02) over 6 mo (FM increasing by a mean 3.0±2.6 kg). Furthermore, LBM actually fell in 6 subjects.
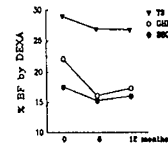
In conclusion, GH Rx in short children results in decreased % BF (most marked in GHD) and increased LBM. Unfavourable fat distribution changes may occur with Rx in SSG children. Rx withdrawal has detrimental effects on body composition in some children over the first 6 mo.

327

CORRELATION OF GH BIOACTIVITY TO IGF-1 AND HEIGHT IN GIRLS WITH TURNER SYNDROME. C.M. Foster, G.B Kletter, N.J. Hopwood, I.Z. Beitins, Department of Pediatrics, University of Michigan, Ann Arbor, MI 48109 USA

To examine the potential causes for short stature in girls with Turner Syndrome, we explored the possibility that secreted GH in these girls may have decreased bioactivity. Twenty girls with Turner syndrome, ages 4.8 to 15.9 years and heights averaging -3.3 by SDS, had blood samples obtained every 20 min for 12 h overnight. An equal aliquot of each sample was pooled for each girl to measure GH by radioimmunoassay (RIA-GH) and estradiol (E2). In each pool, in vivo GH bioactivity was estimated by measurement of the GH-dependent peptides, IGF-1 and IGF-binding protein 3 (IGFBP3). GH bioactivity was also measured in vitro by a newly developed GH bioassay that determined the ability of GH in serum to suppress the conversion of glucose to lipid in 3T3-F442A cultured adipocytes (B-GH; assay sensitivity of 1.25 µg/L GH or 6.25 µg/L GH in serum). Data were analyzed by regression after logarithmic transformation where appropriate. The correlation between RIA-GH and B-GH was 0.519; p = 0.02. IGF-1 and IGFBP3 increased with increasing age but B-GH did not (r = 0.409, 0.695, and 0.017, respectively). The correlation of IGF-1 and B-GH was better than that for RIA-GH (r = 0.375 vs 0.03, respectively). For IGFBP3, the correlations between B-GH or RIA-GH were similar (r = 0.2). Neither B-GH, RIA-GH, IGF-1 or IGFBP3 correlated with height SDS. Four girls had measurable concentrations of E2 and were taller (SDS = -2.4 ± 0.6) than those without detectable E2 (SDS = -3.5 ± 0.3). The girl with the greatest E2 concentration also had the greatest IGF-1, RIA-GH, and B-GH concentrations. In conclusion, B-GH correlates better with IGF-1 than does RIA-GH, and the GH secreted in girls with Turner syndrome is bioactive as determined by in vitro measures (GH bioassay in adipocytes) and in vivo measures (IGF-1 and IGFBP3).

● 328

BOTH THE LOW AND THE HIGH AFFINITY NERVE GROWTH FACTOR RECEPTORS (NGF-R) ARE EXPRESSED IN PANCREATIC BETA CELL LINES. A. Tazi[1], R. Scharfmann[1], M. Asfari[2], M. Polak[2], and P. Czernichow[2].[1] INSERM U120 and [2] Department of pediatric Endocrinology Hopital R. Debre, PARIS FRANCE.

The existence of several homologies between islet and neuronal cells lets us postulate that the factors influencing neuronal differentiation, such as NGF, could also play a role in islet cell differentiation program. As a first step, we have investigated the presence of NGF-R in a panel of beta cell lines such as RINm5F, βTC-1, INS-1. Results obtained were compared to the well characterized neurectodermal PC12 cell line. Binding studies using ^{125}I-NGF revealed that NGF binds specifically to RINm5F cells. Northern blot analysis showed the expression of the low affinity NGF-R (LNGF-R) in RINm5F and INS-1 cells. Reverse PCR using oligonucleotides specific for TRK-A, the neuronal high affinity NGF-R, followed by sequencing, revealed the identity between pancreatic and neuronal TRK-A. By Northern blot analysis, we demonstrated the expression of TRK-A mRNA in all the beta cell lines tested. By immucytochemistry and Western blot, we showed that TRK-A protein was also expressed in these cell lines. In INS-1 cells, expression of TRK-A is as high as in PC12 cells. Finally, when INS-1 cells were incubated with growth hormone (GH), expression of both TRK-A and LNGF-R increased with a maximal induction after 8h incubation.

In conclusion, both the low- and high-affinity NGF-R are expressed in beta cell lines. The control of their expression by GH could represent a possible pathway to explain the role of GH in islet cell development.

329

PRESENCE OF BOTH NEUROTROPHIC GROWTH FACTOR (NGF) AND NGF RECEPTORS (NGF-R) IN RAT ISLET CELLS IN CULTURE: ROLE OF NEUROTROPHIC FACTORS IN ISLET CELL DEVELOPMENT. C. Kanaka, R. Scharfmann and P. Czernichow, INSERM U120 and Department of pediatric Endocrinology, Hospital R. Debre, Paris, FRANCE

NGF and low- or high-affinities NGF-R (LNGF-R and TRK-A), thought to be specific for neuroectodermal cells, have been recently demonstrated on tissues of different embryological origin like fetal kidney, Sertoli cells or ovary. To determine the possible role of NGF in islet cells development, we have studied the expression of NGF- and NGF-R genes in islet cells in culture. Fetal pancreas were cultivated for 5 days and neoformed islets were then mechanically separated from the monolayer of non-endocrine cells. The expressions of NGF, LNGF-R and TRK-A were studied by Northern Blot analysis. Using probes coding for LNGF-R and TRK-A, both types of NGF-R mRNA were identified, which were identical in size (3.8 and 2.8 Kb respectively) to those previously observed in neuronal cells. The TRK-A probe revealed also an as yet unidentified band (.9 Kb), which could correspond to a mRNA coding for a truncated form of the TRK-A receptor. Finally, we demonstrated that RNA coding for the NGF peptide is expressed in the non-endocrine cells, suggesting a possible paracrine mode of action of NGF (possibly secreted by surrounding tissue) on pancreatic islet cells.

In conclusion, the presence of NGF-R in islet cells and the production of NGF by the surrounding non-endocrine cells, adds another homology between beta and neuronal cells and raises the problem of the role of NGF in islet cell development.

330

METABOLIC EFFECT OF GH ON MUSCLE AND FAT TISSUE IN CHILDREN EVALUATED BY MAGNETIC RESONANCE IMAGING (MRI) : RELATIONSHIPS WITH AUXOLOGY.
J. Leger, C. Garel, I. Legrand, A. Paulsen, M. Hassan and P. Czernichow Paediatric Endocrinology and Radiology Dept. Hôpital Robert Debré, Paris, France.

Measurement of muscle (M) and fat (F) tissue surface by MRI was used to study the metabolic effect of GH in children with and without GH deficiency (GHD). 45 prepubertal children with GHD (n = 23), Intrauterine Growth Retardation (n = 14) and Turner's (n = 8) were evaluated before, 3,6 and 12 months after onset of GH treatment (respectively 0.08, 0.23 and 0.11 IU/kg/d). Weight for height was expressed as body mass index (BMI). 7 normal children were followed longitudinally as controls. M and F tissue surface were estimated by MRI of the 2 thighs (one transversal T1 weighted slice, thickness = 8mn, in the middle of the femoral diaphysis). Results were expressed as % change (mean) from baseline values.

	MUSCLE SURFACE			FAT SURFACE			MUSCLE/FAT (ratio)		
Month	+3	+6	+12	+3	+6	+12	+3	+6	+12
GHD	5.2	10.5	16.3	-12.1	-10.7	-6.9	22.2	27.4	28.9
IUGR	15.2	17.4	31.2	-12.5	-14.6	-16.4	34.8	40.3	62.1
Turner's	8.5	10.1	15	-12.3	-14.7	-9.8	25.1	33.2	30.2
Controls	-0.2	3.3	9.1	-3.2	-0.6	7.2	3.4	3.7	2
p Values(vs control)	0.009	0.003	0.01	0.06(ns)	0.005	0.001	0.001	0.0002	0.0009

During GH treatment, a significant increase of M and decrease of F tissue surfaces were observed leading to a dramatic increase of M/F ratio at each time point. This finding remained highly significant when corrected for the small variation of tissue in controls. The M surface increment correlated significantly with height velocity (r=0.45 p=0.004). The BMI decreased significantly and was correlated with M and F tissue surfaces at each period studied (p=0.0001). In conclusion : In children with and without GHD, GH therapy induces rapid and intense variation of M and F tissue. MRI can be used to study some aspects of the metabolic actions of GH.

331

IGF1 AND IGF-BP3 SERUM CONCENTRATIONS ARE LOW AT BIRTH IN INFANTS WITH INTRAUTERINE GROWTH RETARDATION (IUGR) AND ARE NOT PREDICTIVE OF POSTNATAL GROWTH : A LONGITUDINAL STUDY J. Leger, E. Mugnier, M. Noel, A. Paulsen, C. Champion, JM. Limal, P. Czernichow Ped Endocrinology Dept. Hôpitaux Angers and Robert Debré, Paris, FRANCE

This work was undertaken to examine 1) the GH-IGF1 axis in infants with IUGR 2) whether these biological parameters are predictive of postnatal growth pattern. Blood was obtained from 317 IUGR infants (≤ 3d perc. for weight) at birth (cord), 1 and 3 months of life and compared to a control group. Height (H), Weight (W), Head circumference (HC) were followed from birth and during the first 2yrs of life. GH, IGFBP3, IGF1 (after acid gel filtration) were measured by RIA(ng/ml).

Mean ± sem	GH		IGFBP3		IGF1	
	IUGR	Controls	IUGR	Controls	IUGR	Controls
Birth	49±2.8*	20±1.6	1.2±0.98**	1.5±0.06	32.9±1.5*	87.1±5.4
1 month	14±0.7	15±3.8	---	---	74.4±2.2***	102.2±6.8
3 months	6.7±0.5	4.3±1.1	2.2±0.04	2.3±0.1	71.3±2.6	73.8±7.2

At birth, IGF1 and IGFBP3 were decreased and GH increased compared to controls. During the first month of life, a positive correlation (r=0.33) was found between the IGF1 increment and weight gain . All parameters were normalized at 3 months. At 2 years, growth retardation ≤ - 2.SDS was observed in 8 % (H), 12 % (W) and 10 % (HC) of the cases. The risk to be shorter at 2 yrs of age was higher among children with prematurity (37% of IUGR cases). None of the biological parameters at birth was predictive for short stature (≤ -2 SDS) at 2yrs. When the cohort was stratified at birth in 2 groups : asymmetric (45 %) versus symmetric for height (55 %), no differences were found between these 2 groups for biological parameters at birth or height at 2years. In conclusion : Elevated GH levels, low IGF1 and IGF BP3 at birth are strongly in favour of a state of GH resistance due to fetal malnutrition. Height distribution at 2yrs is improved compared to previous historical studies and may reflect the better neonatal care of IUGR infant. *(Supported by Serono-France laboratories).*