

SHORT STATURE IN HOMOZYGOUS β -THALASSEMIA IS DUE TO DISPROPORTIONATE TRUNCAL SHORTENING. C.P. Rodda, E.D.Reid & D.K.Bowden, Department of Pediatrics, Monash University, Monash Medical Centre, Clayton, Victoria 3168, AUSTRALIA

OBJECTIVE: To determine by measuring sitting and standing height, whether growth failure in homozygous β -thalassaemia is disproportionate. **METHODS:** Management of all patients with homozygous β -thalassaemia in the State of Victoria (Australia) is centralised to one major teaching hospital; therefore treatment protocols are relatively standardised, and this group represents a population based cohort. Patients are transfused every 3-4 weeks to maintain hemoglobin values >10 g%, and desferrioxamine 60mg/kg/d, to a maximum of 3g/day, is given S.C. for iron chelation. Measurements were made using Holtain sitting and Harpendon standing stadiometers, in a random sample of 52 of 122 (43%) patients to date. Subischial leg length was determined by subtraction of sitting height from standing height. Standard deviation scores (sds) were used to enable comparisons irrespective of chronological age, and the patient group was analysed according to age: group 1 - <18 y.o., and group 2 - ≥ 18 y.o. **RESULTS:** All results expressed as mean \pm sd. Sitting height was -3.4 ± 1.9 sds (males <18 y.o., n=19), -4.0 ± 1.0 sds (females <18 y.o., n=13); -3.1 ± 1.0 sds (males ≥ 18 y.o., n=10), -3.1 ± 1.4 sds (females ≥ 18 y.o., n=10). Sitting height was significantly different from subischial leg length in both sexes and both age groups ($p<0.0001$) - subischial leg length was -0.1 ± 1.5 sds (males <18 y.o., n=19), -0.5 ± 1.1 sds (females <18 y.o., n=13); 0.9 ± 1.3 sds (males ≥ 18 y.o., n=10), 0.2 ± 1.1 sds (females ≥ 18 y.o., n=10). **CONCLUSION:** Short stature is mainly due to truncal shortening in this patient group. Hypogonadism and chelation therapy are possible etiologic factors.

COINCIDENCE OF NOCTURNAL GROWTH HORMONE AND ZINC SECRETION PROFILES IN SHORT CHILDREN. G.W. Moll, Jr. & G.L. Lin, Department of Pediatrics, University of Mississippi Medical Center, Jackson, Mississippi 39216.

A subgroup of short children grow in response to Zinc (Zn) which is an important cofactor in many enzymes essential to basic metabolism. Zn binds to a number of serum proteins; Zn is reported to bind to Growth Hormone (GH) and thereby exponentially assist GH binding to a receptor protein. We here report our test of the hypothesis that GH secretion is closely associated with Zn secretion in short children who do not have classic GH or Zn deficiency.

Seven short (<5 th height percentile for age) children, 4 females (F) & 3 males (M), were admitted with informed consent to our CRC for blood sampling every 30min during a full night of sleep (11pm-7am). All subjects had demonstrated GH release >10 ng/ml to short term GH testing and showed no evidence of a metabolic, dysmorphic or genetic disorder. We also evaluated a male (MX) with GH deficiency due to a Rathke Pouch Cyst. Plasma was carefully collected to avoid hemolysis and analyzed for GH (Nichols IRMA kit) and Zn (Atomic Absorption) content. Data for each subject were evaluated with assistance of Dr. Van Cauter's computer program (ULTRA) to identify GH and Zn pulses and their coincidence within a 30min interval.

	GH sum(range)ng/ml	Zn sum(range)mcg%	#GH pulses	#Zn pulses
F1	294 (2-34)	1323 (70-87)	4 *	4
F2	104 (0-25)	1258 (74-91)	3 *	4
F3	47 (0-8)	1351 (70-84)	4 *	5
F4	113 (0-25)	1399 (45-106)	4 *	5
M1	62 (1-11)	1653 (75-140)	3 *	4
M2	177 (0-35)	1494 (70-116)	5 *	5
M3	136 (0-30)	1611 (72-120)	4 *	5
(MX)	2 (0-0.2)	1601 (78-122)	1 *	4

* All GH pulses coincident with Zn
There was no significant correlation between individual sums of GH & Zn ($r^2=0.14$). These data support the hypothesis that the release of endogenous Growth Hormone is associated with a release of Zinc.

INSULIN-LIKE GROWTH FACTOR BINDING PROTEINS FROM PRIMARY CULTURES OF RAT OVARIAN THECA-INTERSTITIAL (ROTI) CELLS: REGULATION BY LH AND IGF-I. J. F. Cara and J. Fan, Dept. of Peds., University of Chicago Pritzker School of Medicine, Chicago, IL 60637, USA

We and others have shown that insulin-like growth factor-I (IGF-I) and IGF binding proteins (IGFBPs) play an important role in ovarian function. In the present study, we tested the hypothesis that ROTI cells produce IGFBPs and that theca-interstitial cell IGFBP production is regulated by LH and IGF-I.

Density gradient-purified ROTI cells were cultured in serum-free medium with selected concentrations of LH or IGF-I, alone and in combination. After 24 to 48 hours, supernatant media were removed and IGFBPs analyzed by Western ligand blotting and immunoblotting. Ligand blotting was carried out using equal amounts of radiolabeled IGF-I and IGF-II. Immunoblotting was carried out using anti rat IGFBP-3 antiserum and anti bovine IGFBP-2 antiserum (provided by Drs. Nicholas Ling and David Clemmons, respectively).

Western ligand blotting of media obtained from cells cultured without added hormones (Control) revealed a predominant IGFBP of 29-30 kD with minor species of 28 and 35-40 kD. Immunoblotting with anti-IGFBP-2 detected the 29-30 kD species whereas immunoblotting with anti-IGFBP-3 failed to detect any IGFBP-3. High doses of LH (100 ng/ml) decreased IGFBP-2 expression while 100 ng/ml IGF-I increased IGFBP-2 levels 5 to 10-fold above control values. IGFBP-2 levels were increased by 24 hours and reached peak levels by 48 hours of incubation.

We conclude that rat ovarian theca-interstitial cells produce several IGFBPs, primarily IGFBP-2. IGFBP-2 levels are increased by IGF-I and suppressed by high doses of LH. The production of IGFBP-2 by theca-interstitial cells and its regulation by LH and IGF-I may play an important role in ovarian androgen production.

REDUCED EXPRESSION OF THE HEPATIC GROWTH HORMONE (GH) RECEPTOR IN EXPERIMENTAL UREMIA. B. Toenshoff, B. Carlsson, E. Weiser, A.C.A.F. Robinson, W.F. Blum, S. Eden, O. Mehls. Univ.-Children's Hosp. Heidelberg & Tuebingen, FRG; ¹Department of Physiology, Univ. of Goeteborg, Sweden; ²National Institute for Medical Research, London, U.K.

In uremia reduced longitudinal growth and decreased hepatic IGF-I secretion despite elevated GH serum levels point to a resistance to the action of GH, which could be a consequence of a reduced hepatic GH receptor (R) expression. To address this hypothesis we studied the hepatic GH-R mRNA content in uremic female SD rats (n=7 per group) subjected to 5/6 nephrectomy (U) compared to sham operated pairfed (PC) or ad libitum fed (aLC) controls. Animals were treated with 10 IU rhGH/kg/day, or solvent for 10 days. Total RNA was prepared from rapidly frozen liver tissue and the GH-R mRNA quantified by solution hybridization. Mean (\pm SD) weight gain was lower in U (21.4 ± 7.9 g) compared to PC (24.1 ± 5.9 ; $P<0.005$) and aLC (33.5 ± 6.3 ; $P<0.005$). Hepatic GH-R mRNA was reduced in U (0.79 ± 0.39 amol/ μ g DNA) vs PC (1.46 ± 0.32 ; $P<0.005$) and vs aLC (2.66 ± 0.73 , $P<0.001$). Exogenous rhGH slightly increased (n.s.) GH-R mRNA in all groups. Plasma GH binding protein (BP) levels (RIA) in U were 11.1 ± 4.4 ng/ml, in PC 8.2 ± 2.3 , in aLC 5.7 ± 2.5 ($P<0.01$). We conclude that experimental uremia is accompanied by a marked reduction of hepatic GH-R expression. The data in the pairfed animals indicate that this effect is only partially attributable to malnutrition. Increased plasma GHBP levels in U might be interpreted as a consequence of reduced renal clearance.

INTERLEUKIN-1 DIFFERENTIALLY STIMULATES INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 3 RELEASE FROM HUMAN ARTICULAR CHONDROCYTES. R.C. O'Leary, M. Mohtai, D.M. Wilson, and R.L. Smith. Departments of Pediatrics and Orthopedics, Stanford University, Stanford, CA 94305, USA.

Articular chondrocytes create and maintain articular cartilage and their growth and metabolism are tightly regulated. The insulin-like growth factors (IGFs), and hence the IGF binding proteins (IGFBPs), play a significant, but unclear, role in this regulation. We examined the articular chondrocyte release of IGFBPs under conditions that simulate inflammation. Human chondrocytes were isolated from articular cartilage obtained post-mortem from a three year old female. The cells were grown in serum free conditions in high density monolayers. Interleukin-1 (IL-1), a central mediator of the inflammatory response, was added to a final concentration of 30 ng/ml and cultures incubated for 4, 12, 24, or 48 hours. Conditioned media were analyzed for IGFBPs by Western ligand blotting, autoradiography, and laser densitometry. Conditioned media from unstimulated chondrocytes contained IGFBPs at 22, 27, 38, and 41 kDa and their concentrations increased linearly over 48 hours. The 38/41 kDa doublet has been shown in serum to be IGFBP-3. Conditioned media from the IL-1 stimulated chondrocytes contained the same forms of IGFBP, plus a 34 kDa IGFBP at 48 hours. The rate of accumulation of the IGFBP-3 doublet from the IL-1 treated chondrocytes was 3.1 ± 0.4 (SE) times the rate from the unstimulated chondrocytes ($P<0.05$). The rates of accumulation of the 22 and 27 kDa bands were not different. IGFBPs are produced by human chondrocytes *in vitro*, and IL-1 differentially increases the rate of accumulation of IGFBP-3. IGF-I has profound effects on articular chondrocytes *in vitro*, and may play a role in articular cartilage disease. The finding that chondrocytes increase the release of an IGFBP in response to the cytokine IL-1 supports this hypothesis.

SERUM GH-BINDING PROTEIN BEFORE AND AFTER LIVER TRANSPLANTATION IN CHILDREN WITH CONGENITAL BILIARY ATRESIA. C. Yamanaka, S. Uemoto*, K. Tanaka*, H. Kato*, S. Fujita*, K. Ozawa*, T. Momoji and H. Mikawa, Department of Pediatrics, and Department of Surgery*, Kyoto University Faculty of Medicine, Kyoto, Japan

Changes of serum GH-binding protein (GHBP) levels in children with congenital biliary atresia were studied before and after living related liver transplantation (LT). Of 6 children, 3 showed growth retardation (less than -2 SDS of height) before LT. All of them were free from post-operative complication. Steroids were discontinued within the first 3 months. Blood samples were drawn before LT, 1, and 6 months after LT for determination of GHBP levels (ligand mediated immunofunctional assay) and plasma IGF-I levels (RIA, direct method). Preoperative GHBP levels were reduced for their age in 3 of the 6 patients, and IGF-I levels were less than 0.22 U/ml in all 6 children. No correlation was found neither between preoperative height SDS and preoperative GHBP level, nor between the former and preoperative IGF-I level. In the three children with decreased GHBP levels preoperatively, GHBP levels increased markedly a month after LT and stayed normal at 6 months. In the remaining 3 children with normal preoperative GHBP levels, two showed normal values throughout the observation period but one showed reduced serum GHBP level at 6 months after LT. Post-transplantation IGF-I levels were more than 10 times at one month and more than 4 times at 6 months compared with those of pre-transplantation in all but one patient. Height SDS evaluated at 6 months improved in 5 of 6 children. The patient who showed reduced GHBP level could not undergo postoperative catch-up growth in spite of the increased IGF-I level at 6 months. These findings suggest that the increase of GHBP and IGF-I after liver transplantation might reflect the regeneration of transplanted liver as well as the metabolic improvement. Long term observation would be necessary for evaluation of GHBP as an indicator of catch-up growth after liver transplantation.