●446 LIPOPROTEIN RESPONSE TO 5α-DIHYDROTESTOSTERONE(DHT) AND TESTOSTERONE(T) IN MACACA FASCICULARIS.

Nancy G.Greger, William Insull, Jeffrey Probstfield, Bruce S. Keenan. Baylor College of Medicine, Depts. of Pediatrics and Internal Medicine, Houston, TX.

A decrease in high density lipoprotein cholesterol (HDL_C), one of the major risk factors for coronary artery disease, occurs during puberty in males. Previous studies have shown this effect with T therapy for adolescent males at puberty (Kirkland, RT, et al; JAMA, in press). The mechanism of action is unknown.

Two adult male monkeys (Macaca fascicularis) were studied to determine simultaneous changes in plasma androgens and HDL_C during 5 phases- Precastration(C_i); Postcastration(C_X); C_X & T therapy; C_X & DHT; C_X, T & 5α-reductase inhibitor (4-MA, Merck, 2-5mg/kg). Normal ranges for T, DHT, HDL_C for this species were established. After C_X, androgens decreased and HDL_C increased significantly. Therapy with T and a nonaromatizeable androgen(DHT) after C_X both produced a significant decrease in HDL_C. Simultaneous therapy with T and 4-MA did not increase HDL_C from C_X+ T levels.*

		HDL_C (mg/dl) + SE			
	C_i	C_X	C_X & T	C_X& DHT	C_X& T & 4-MA
MONKEY A	57.0±1.8	66.6±2.2 (P<0.005)	48.0±5.0 (P<0.010)	47.5±1.5 (P<0.005)	55.7±1.9 NS*
MONKEY B	62.9±1.6	80.2±1.7 (P<0.001)	43.5±0.5 (P<0.001)	44.5±3.5 (P<0.001)	57.3±0.3 NS*

This primate model shows hormone responsive lipoprotein changes similar to humans. 5α-reductase and aromatase (estrogen) activity do not appear to be necessary for this response. This model will allow further study of the mechanism of action and benefits or side effects of therapeutic intervention with antiandrogens.

●447 ADRENOLEUKODYSTROPHY MAY RESEMBLE FAMILIAL ACTH UNRESPONSIVENESS.

Carol S. Hart, Stephen M. Rosenthal, Susan Shaw-Reines, Selna L. Kaplan, Melvin M. Grumbach, University of California, San Francisco, Dept. of Pediatrics, San Francisco

Adrenoleukodystrophy (ALD) is a well-described cause of familial primary adrenal insufficiency in which neurological symptoms may be absent for many years. While the spectrum of adrenal insufficiency in ALD is variable, primary impairment of glucocorticoid secretion may resemble familial ACTH unresponsiveness, a different rare form of adrenal insufficiency. To distinguish ALD from other forms of familial adrenal insufficiency, we carried out the following studies in 3 male patients (age 11-16 yr): measurement of plasma saturated very-long-chain fatty acids (C26 and C26/C22 ratio), adrenal antibodies (AAb), plasma renin activity (PRA), and computerized tomography (CT) or magnetic resonance (MR) studies of the CNS. C26 was elevated above control in all three patients, 2.14 ± 1.21 μg/ml, mean ± S.D. (normal 0.33 ± 0.18) as was the C26/C22 ratio, 0.04 ± 0.01 (normal 0.01 ± 0.01), consistent with the diagnosis of ALD. AAb were undetectable in all patients. PRA was normal in one patient and elevated in two. Neurological examinations were unremarkable in all patients, without evidence of leukodystrophy on CT or MR scans. This study illustrates the need to consider ALD in the differential diagnosis of childhood familial primary adrenal insufficiency in the absence of neurological symptoms. Furthermore, it is important to recognize that ALD may present with isolated glucorticoid deficiency and thus may mimic ACTH unresponsiveness, which has separate genetic, prognostic, and therapeutic considerations.

448 ACTIVATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL (HPG) AXIS IN PRETERM FEMALES.

Lynn A.Hawkins, Sandra L.Blethen, Andrew M.Steele, Fred I.Chasalow. Sch of Med, SUNY Stony Brook, Schneider Children's Hospital of LIJMC, Dept of Peds, New Hyde Park, NY.

Precocious puberty was observed in a preterm (27 wks post-conceptional age - PCA) female. At 41 wks PCA, estradiol (E2) levels were elevated (282 pg/ml). By 13 months PCA, E2 decreased spontaneously (18 pg/ml) and pubertal changes regressed. However, pelvic ultrasonography revealed the development of ovarian cysts. In order to interpret these findings and determine their significance, we studied 6 normal preterm female infants (PCA ≤34 wks) during the first month of postnatal life. We measured: a) E2 - max > 30,000 pg/ml on day of birth (DOB), b) LH - max 196 mIu/ml on DOB, c) FSH - max 125.2 mIu/ml 3 wks after birth, d) 17-hydroxyprogesterone - max 4320 ng/dl on DOB, and e) DHEA-S - max 429 μg/dl on DOB. As in full term infants, E2 was highest on the DOB and decreased to prepubertal values within 1 month. In contrast, gonadotropin levels were variable but remained elevated throughout this period. Conclusions: Although in most preterm females elevated gonadotropin levels persist for at least 1 month, the same is not true for E2. These data suggest that the HPG axis is activated in premature female infants prior to their would be term delivery. The index case differed in that elevated E2 levels persisted and ovarian cysts developed.

●449 SUPPRESSION OF GROWTH HORMONE AND THYROID HORMONE ASSOCIATED WITH VALPROIC ACID THERAPY.

Carol A. Huseman, Richard D. Torkelson, University of Nebraska, University of Nebraska Medical Center, Departments of Pediatrics and Neurology, Omaha, NE.

Valproic acid (VA) is a commonly used anticonvulsant. One proposed mechanism of action for VA is enhancement of central GABAergic tone by inhibition of GABA transaminase. We report suppression of somatic growth, hGH, and thyroid function in 5 girls, ages 2-14 years, maintained o therapeutic VA serum levels (60-120 ug/ml) for 15-84 months.

Endocrine Data During and After Treatment

Pt.	CA (yrs)	On VA (mos)	Ht/Wt (cm/kg)	Maximum hGH (A*)	(B*)	Free T_4/TSH (0.6-1.8/<6)	Cortisol (7-20)	SMC±SD **
1	2.0	15	77/ 7	1	0.7	0.7/1.6	15	**0.33±.05**
	6mo off VA		81/ 9	8	9.4	1.6/1.9	21	0.54±.02
2	13.6	60	154/35	10	3.6	1.2/2.4	12	**0.77±.10**
	3mo off VA		156/38	26	13.2	1.3/1.4	13	2.2
3	4.4	42	97/12	7	1.7	1.1/1.2	14	**0.31±.07**
	5mo off VA		99/13	24	1.6	1.1/1.3	15	0.94±.07
4	14.4	84	/20	2	9.3	0.5/2.4	12	**0.27±.06**
	6mo off VA		/21	33	42.4	1.5/1.4	7	1.38±.10
5	4.8	34	93/14	3	2.8	1.4/1.7	12	0.45
	4mo off VA		96/15	16	3.4	1.9/1.2	7	0.45±.01

*Normal values (A) and (B) > 10 **Somatomedin-C = Abn in Bold

All children showed suppressed hGH values to L-Dopa(A) or insulin(B) testing during VA therapy. hGH responses, Free T_4 and SMC values normalized with concomitant increases in growth velocity after VA was stopped. Summary: Chronic VA therapy can suppress hGH, T_4, SMC, and inhibit growth. This effect may be due to exhaustion of the stimulatory effect of GABA on the somatotrope or thyrotrope during chronic VA therapy. Growth must be carefully monitored in all patients on VA therapy.

▲450 THE DIFFERENTIAL EXPRESSION OF INSULIN-LIKE GROWTH FACTOR mRNA IN TWO RAT TUMOR CELL LINES.

Philip M James, ML Cleary, A Hoffman, RL Hintz and RG Rosenfeld, Dept. of Pediatrics., Stanford University Medical Center, Stanford, CA.

Buffalo Rat Liver 3A (BRL) and 18,54-SF cells are two rat tumor cell lines which have been maintained continuously in serum-free media. Both cell lines secrete rat IGF-II (>50ng/ml in three day conditioned media) and have no detectable rIGF-I peptide by RIA. The experimental design was to: 1) demonstrate that lack of rIGF-I production was due to absent transcription of rIGF-I mRNA, and 2) to compare BRL, 18,54-SF and rat liver IGF-II RNA sizes and abundance patterns on Northern blots. RNA was prepared by the guainidine thiocyanate/LiCl technique. Polyadenylated RNA (A+) was separated from non-polyadenylated RNA (A-) by oligo dT cellulose chromatography, sized on formaldehyde-agarose gels and transferred to nylon membranes. IGF RNA sequences were detected either by hybridization to *in vitro* transcribed cRNA specific to each strand, or to *in vitro* hexamer primed DNA at a specific activity > 10^9 cpm/μg. Probes were to i) the carboxyl terminal E peptides and 3' nontranslated regions which are highly specific for each of the two IGF species and ii) the 5' region of IGF-I thus allowing detection of both IGF-I splicing variants. Non-specific binding was reduced by final washing in 0.1x SSC at 62C. IGF-I mRNA could not be detected in BRL nor 18,54-SF cells but was easily detected in adult rat liver as 1800 and 660 base major species with ~6 intermediate forms. IGF-II mRNA was detected by the 3' cDNA and 3' anti-sense cRNA probes; no species were found to hybridize with the 3' sense cRNA, indicating that all mRNAs are in the usual 5' to 3' sense orientation. The BRL and 18,54-SF cells had multiple IGF-II forms (>10kb, 7.0kb, 5.8kb, 4.4kb, 3.5kb, 3.0kb, 2.7kb, 2.5kb, 1.8kb and 1.1kb). The most abundant form in BRL cells was 5.8kb in length and polyadenylated. The predominant form in 18,54-SF cells was 4.4kb in length and this was the most abundant A+ form; additionally an A- form at 1.1kb was observed. Adult rat liver had no detectable IGF-II RNA sequences. These data demonstrate that regulated expression occurs at the level of transcription. The presence of rIGF-II mRNA and peptide in the absence of rIGF-I mRNA and peptide, coupled with the ability to grow in serum free defined media support IGF-II as being a critical growth factor in these cell lines.

●451 GLUCOCORTICOIDS REGULATE ADRENAL OPIATE PEPTIDES

E.F. La Gamma, J.E. Adler, & I.B. Black. Pediatrics & Neurobiology, SUNY at Stony Brook, and Division of Developmental Neurology, Cornell Medical Center, New York.

Glucocorticoids regulate sympathoadrenal catecholamine (CA) biosynthesis. We determined whether co-localized adrenal opiate peptides are also subject to hormonal control. Adrenal cortical destruction (mitotane) decreased baseline leu-enkephalin (LEU) levels *in vivo* by 38% ($p<0.05$). To examine cellular mechanisms, rat medullae were grown as explants in glucocorticoid deficient medium. LEU levels start low then increase in a dose-dependent fashion following corticosterone replacement (zero to 10^{-5}M). Effects of glucocorticoids could be blocked by alkylating (CM-21, DM-21) or non-alkylating (cortexolone) receptor antagonists added to corticosterene containing medium. Moreover, inhibition of glucocorticoid receptor translocation to the nucleus (cytochalasin B) also blocked the hormone effect. In addition, a 13 out of 17 nucleic acid match for a putative glucocorticoid receptor binding site was identified in intron A of the rat preproenkephalin genome. These observations are consistent with dual hormonal, and transsynaptic regulation (La Gamma, et al PNAS 82:8252, 1985) of opiate biosynthetic processes. Therefore, similar to CA, LEU exhibits significant transmitter plasticity which may serve an adaptive role in modulating complex biochemical and behavioral responses (eg. during stress or development) with exquisite precision.

Supported in part by the American Heart Association.