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K.Herkner*, W.Swoboda
Ludwig Boltzmann Inst.f.Pediatric Endocrinology c/o Univ. Kinderklinik, Vienna, Austria

CLASSIFICATION OF CRYPTORCHIDISM BY MEANS OF 5β-ANDROSTAN-3α,17β-DIOL EXCRETION.

This study is based upon the hypothesis that cryptorchidism can be accompanied by moderate target organ unresponsiveness to androgens, which is best reflected by specific metabolites, i.e. 5α-androstan-3α,17βdiol (5αD) and 5β-androstan-3α,17βdiol (5βD). We suggest the latter to be a marker for the degree of genital development. In addition, the excretion of testosterone (T), dihydrotestosterone (DHT) and androstenedione (AN) was analysed. T+AN was interpreted as "androgenic pool". Excretion profiles were analysed by capillary gas chromatography, serum T by RIA. Data were evaluated before and after a three days hCG stimulation. 21 boys (age 2-14 yrs) were examined. 7 boys with retractile testicles served as "controls" (group I). For classification purposes the stimulation ratio F (=day3 over day0) was used. Three different groups could be distinguished:

	(urinary excretion)				(serum)
	F:5αD	F:5βD	F:DHT	F:T+AN	T
group I	1.0-8.9	2.2-6.3	ND	0.9-1.1	3.0-15.2
group II	0.8-3.5	1.1-2.3	0.8-1.5	1.0-1.7	1.2- 5.6
group III	0.4-1.4	0.4-0.8	0.0-2.5	0.9-3.3	0.8- 1.5

Group II was called "intermediate" and cases of anorchia were found in group III. Correlation with clinical findings suggest that F:5βD might be the most useful addition to the classical diagnostic procedures. We speculate that the extended analyses might provide some aspects for clinical prognoses.

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P. Calzi*, L.Gargantini, G.Nizzoli*, F. Braggion*, G.Chiumello
Scientific Inst. H San Raffaele, Dept. of Pediatrics, Endocrine Unit, University of Milan, Italy.

SPIRONOLACTONE COMBINED TO AN ESTRO-PROGESTAGEN IN ADOLESCENTS AFFECTED BY HIRSUTISM.

Almost 5% of women is affected by irsutism and about 56% of these subjects start complaining on some signs during the adolescence period in which a considerable anxiety is connected with the body image. After having excluded Cushing's syndrome, CAH late onset, ovarian and adrenal tumours, we treated six adolescents (mean age 16yr 1mo) affected by hirsutism (Hatch's score $\geq$ 10) with 100 mg/daily of spironolactone for 12 months (200 mg/daily with score > 20 or therapeutical unsuccess after 6 months of therapy). To all subjects was added an oral contraceptive (0.15 mg of desogestrel + 0.03 mg of ethinil -estradiol) to obtain regular withdrawal bleeding and contraception effect. To make a correct evaluation of the data, we excluded from the study those areas treated by esthetic treatment. Clinical and hormonal evaluations (FSH, LH, PRL, T, DHEAs) were obtained before and after 3-6-9-12 months of therapy. During follow-up no change was demonstrated in hormone levels; the mean score significantly decreased after 3 months of therapy ($p < 0.01$) and at every specific control ($p < 0.001$). In one girl, 6 months off-therapy, no sign of hirsutism was demonstrated. No significant side-effects were noted in our patients. Spironolactone combined to an estro-progestagen is an effective and well-tolerated approach to the management of hirsutism in adolescents.

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P.J. Pringle*, P. Hindmarsh* & C.G.D. Brook
Endocrine Unit, The Middlesex Hospital, London

24HR GONADOTROPHIN PROFILES IN NORMAL CHILDREN

Using a precise immunoradiometric assay for LH and FSH we have measured gonadotrophin concentrations in 24 hour profiles of 30 children aged 5.8 - 15.5 years.

A rise in gonadotrophin concentration was seen in 73% of prepubertal children between 1600 and 0030 hours. LH concentrations were greater than FSH, but no clearly defined periodicity of LH secretion could be discerned.

During puberty, the pattern of gonadotrophin secretion changed progressively. Nocturnal pulsatility (periodicity 90 minutes) appeared at breast stage II and 24 hour gonadotrophin secretion at breast stage IV.

This study demonstrates that gonadotrophin secretion at a low level is detectable long before the clinical onset of puberty. Although sex steroid concentrations were below the limit of detection of current assays, they may be important in determining the change in GH pulse frequency we have previously described to be coincident with the mid-childhood growth spurt. When gonadotrophin secretion achieved regular periodicity, sex steroid concentrations rose, pubertal changes occurred and the growth spurt was entrained. 24 hour gonadotrophin secretion was required for the attainment of reproductive capability.

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F.C.W. Wu*, G.E. Butler*, R.F. Walker*, D. Riad Fahmy*, C.J.H. Kelnar
MRC Reproductive Biology and Cytogenetics Unit, Royal Hospital for Sick Children, Edinburgh and Tenovus Institute, Univ. of Wales, Cardiff, U.K.

ORAL TESTOSTERONE UNDECANOATE IN THE INDUCTION OF MALE PUBERTY

Oral testosterone undecanoate (TU) was used in 5 untreated prepubertal (G1PH1) boys (aged 12.1-17.1 yr) with hypogonadism and delayed puberty. The aim was to induce puberty by mimicking the pubertal diurnal variation of testosterone (T) thus achieving optimal growth and virilisation without disproportionate skeletal maturation. TU 40 mg was administered daily after a standard breakfast for 6 months. Plasma and salivary T levels were monitored for 10 hours with the first dose and repeated at 3 and 6 months. After 6 months, pubertal ratings had progressed to G2-3/PH1-3 with no significant change in testis size. Mean height velocity increased from 3.40±0.63 to 7.10±0.95 cm/yr. Advance of BA/CA ratio was 0.95±0.40. Peak and mean total T declined at 3 and 6 months. Mean free T index increased at 6 months but peak free T index was not significantly altered as a result of the SHBG fall. Salivary T and plasma T profiles were closely correlated being within the range for G4. Satisfactory initiation of puberty can be achieved with oral TU. Apparently high total T peaks observed at the start of treatment reflected prepubertal SHBG concentrations but free and salivary T levels produced by 40 mg TU were appropriate for mid to late puberty. Careful monitoring of treatment and individual dosage adjustment are indicated.

MONTH	PEAK T (nmol/l)	MEAN T (nmol/l)	PEAK FTI	MEAN FTI	SHBG (nmol/l)
0	39.7±7.6	13.9±4.8	61.2±27.7	19.6±5.4	77.4±39.6
3	25.4±10.4***	9.2±3.7**	71.6±37.4	25.0±10.1	40.1±20.1*
6	24.4±6.3**	9.5±2.9**	82.1±27.8	31.2±7.7**	32.3±12.5*

(Mean ± SD) * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ vs Month 0

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Henriette A. Delemarre-van de Waal
Department of Pediatrics, Acad. Hospital of the Vrije Universiteit, Amsterdam, The Netherlands

PUBERTY CHANGES THE GONADOTROPIN RESPONSE TO NALOXONE INFUSION

Naloxone, an opioid antagonist, increases LH/FSH blood levels in adults. The absent response in prepuberty may be caused by an insensitive, unstimulated pituitary. Therefore we studied LH/FSH secretion during naloxone infusion before and after LHRH priming. Protocol: three prepubertal boys aged 13.1-14.6 yrs (BA 10.4-12.3), Testosterone (T) 0.4-0.9 nmol/l, received LHRH 20 µg/1.7m² every 90 min iv during 42 hrs. Before as well as 7 days after pulsatile LHRH treatment naloxone was infused iv from 10.00-13.00h 2 mg/-1.7m²/h. At 13.00h a LHRH test was performed. LH and FSH was measured from 9.00-15.00h at 15 min intervals. In 2 pts the study was repeated in a pubertal stage (G3).
Results: in all three prepubertal boys naloxone did not elicit an increase of LH or FSH, neither before nor after LHRH priming, while the LH and FSH response to the LHRH test had distinctly increased after LHRH priming. In the 2 pubertal boys basal LH and FSH were within the same range; T was 4.5 and 13 nmol/l. Naloxone induced a clear LH increase with two LH pulses only in the boy with a T of 13 nmol/l, before as well as after LHRH priming.
Conclusion: naloxone cannot induce a LH/FSH increase in prepuberty even not after LHRH priming; in puberty an increase can be elicited. Therefore the opioids take no major part in the LHRH "intrinsic restraint" during prepuberty, but play a role in the sex steroid negative feedback, which becomes operative during puberty.

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JP Bourguignon, A Gerard*, C Charlet-Renard*, P Franchimont*.
Department of Pediatrics and Radioimmunoassay Laboratory, University of Liège, Belgium.

STIMULATION OF GnRH SECRETION BY N-METHYL-D, L-ASPARTATE (NMA) IN VITRO AND IN VIVO.

In several species, IV or SC administration of NMA, a neuroexcitatory analog of aspartate, elicits a pulse of LH secretion. In prepubertal monkeys, chronic intermittent administration of NMA induces pubertal development through a putative hypothalamic action (Plant TM et al, Endocrine Soc. Meeting, 1987, Abst. 65). In order to get a direct insight into this mechanism, GnRH release from the rat hypothalamus was studied in vitro in the presence of NMA. Concentrations $\leq$ 0.74 mg/ml were not effective. Incubation with NMA 1.47 mg/ml for 7.5 min resulted in an increase of GnRH release from 11.5 ± 4.3 to 36.2 ± 14.1 pg/0.5 ml (mean ± SD, n = 12). The effect of NMA in vivo was evaluated by studying rats sacrificed at different times after SC injection of 30 mg/kg of NMA. One, 3, 5, 7.5 and 10 min after NMA injection, mean serum LH rose progressively (32.0, 38.0, 70.0, 71.0 and 87.5 ng/ml, respectively). The hypothalami of these rats were immediately dissected and studied in vitro. One, 3, 5, 7.5 and 10 min after NMA injection in vivo, mean GnRH release in vitro showed a marked increase (20.0, 32.0, 46.3, 115.5 and 41.8 pg/0.5 ml, respectively), indicating that GnRH is likely the neuroendocrine mediator of NMA-induced LH secretion. The study of GnRH release by NMA in vitro provides a means to further elucidate the mechanisms of the hypothalamic pulse generator and its role in the initiation of puberty.