125

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BREAST CONTACT THERMOGRAPHY IN DIFFERENTIAL DIAGNOSIS OF PREMATURE THELARCHE AND PRECOCIOUS PUBERTY.

In order to contribute to the differential diagnosis between idiopathic Premature Thelarche (PT)and true Precocious Puberty (PP) we performed Breast Contact Thermography (BCT, cholesteric liquid crystal plates) in 13 girls with PT and 12 with PP (previously diagnosed) and in 105 control girls (Tanner's B1-5). We evaluated the 4 principal components (fundus, vascularization, nipple and periareolar heat changes). Arbitrary gradual scores (0,1,2...) were attributed to the maturative signs. A Thermographic Index (TI= sum of the 4 scores of a single breast) and the higher TI (hTI= between the 2 breasts of single girls) were calculated.

Results: in controls, single scores, TI and hTI had a positive correlation (r, $p < 0.001$) with B stages. In PT, all signs of vascularization were always (100%) absent, while in PP they were always present, although in some cases monolaterally. The TI of PT was not different from B1 girls and significantly lower ($p < 0.001$) than PP girls and B>1 controls. The hTI ranged from 0 to 3 in PT, from 4 to 13 in PP girls.

We conclude that low hTI (≤ 3)and no signs of vascularization indicate PT, while vascular hyperthermia and hTI ≥ 4 indicate PP. We emphasize the useful diagnostic aid of the noninvasive imaging technique of BCT in evaluating the pathophysiology of pubertal breast development.

126

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SPECIFIC ANDROGEN BINDING IN HUMAN FETAL EPIPHYSEAL CHONDROCYTES IN CULTURE .

Human fetal epiphyseal chondrocytes were obtained in primary culture (Ped. Res. 19:720,1985) . In this system testosterone (T) was metabolized into androstendione and dihydrotestosterone (DHT) (J. Clin. Endocrinol. Metab. 58:819,1984) and we have recently shown that DHT significantly stimulates chondrocyte proliferation .

In order to study the mechanism of androgen action on human fetal epiphyseal chondrocytes , cells have been incubated with DHT-3H (0.1 - 9 x 10^{-9} M) with and without 200-fold unlabelled DHT for 30´at 37ºC . Cells were sonicated in Tris 0.02M-HCl pH=7.5 , 0.5 M KCl , 1.5 mM EDTA , 2 mM Mercaptoethanol . Unbound DHT was separated with DCC Buffer . Maximal binding capacity and Kd were calculated according to a Scatchard plot . In chondrocytes from fetuses (20-40 weeks-old ; 4 ♂ and 4 ♀) Bmax in ♂ is 4.2 ± 1.2 fmol/mg Prot. and in ♀ 5.5 ± 0.5 ; Kd is 0.34 ± 0.14 nM in ♂ and 0.65 ± 0.21 in ♀ . No difference was found for sex nor for gestational age .

Human fetal epiphyseal chondrocytes in primary culture seem therefore to present proteins which may act as typical specific androgen receptors . These results suggest that biological activity of androgens on human fetal epiphyseal chondrocytes in culture may be mediated through specific receptors .

127

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ANDROGEN INSENSITIVITY (AI) IN 43 PATIENTS: CLASSIFICATION BASED ON CLINICAL AND ANDROGEN RECEPTORS (AR) PHENOTYPES.

Androgen binding was studied in genital skin fibroblasts (GSF) established from XY patients with testes displaying signs of complete androgen insensitivity syndrome (CAIS, n = 14) and partial AIS (n = 29). Total whole-cell AR concentration (Bmax) in GSF strains derived from 31 normal circumcised boy's was 775 ± 185 x 10^{-18} mol/µg DNA (mean ± SD). The AR phenotype was receptor-negative in 79% of CAIS patients; however, the remaining 21% in this series had supranormal AR concentrations (mean 1840, range 1541 - 2072 x 10^{-18} mol/µg DNA). Further studies on these cell strains showed stable androgen binding at 40ºC, normal dissociation rate for the AR complex, appropriate GSF cytosol sedimentation on sucrose density gradients in the presence of molybdate and 60% binding of the androgen ligand located in the nuclei. Only 7% of GSF strains from patients with PAIS were AR-negative; mean ± SD concentration of AR in the remainder was 837 ± 315 x 10^{-18} mol/µg DNA. No PAIS cell strain contained a supranormal AR concentration. More than 90% of AR-positive cell strains (including those with supranormal AR levels) responded by further augmenting total cellular AR concentration following prolonged androgen preincubation of GSF. This AR phenotype is not the result of a mutation affecting the gene coding for the AR protein.

128

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SEX HORMONE BINDING PROTEIN (SBP) AS A MARKER OF ANDROGEN SENSITIVITY IN INFANTS AND CHILDREN.

Establishing a reliable test of androgen sensitivity is still prerequisite for etiological diagnosis in infants suspected of androgen insensitivity syndrome (AIS). Since androgens are known to decrease SBP levels we have investigated the possibility of using plasma SBP as a marker of androgen sensitivity, and studied the conditions for a rational protocol. The ontogenic pattern of SBP from birth to adulthood was first established in 695 controls, (by a solid phase method). SBP levels (µg/l) low at birth, (6.3±3) rise to 22.3±7.5 during the first month of life correlatively with time, with no sex difference but large individual variations. In addition, SBP decreased significantly after either an acute or a 3-day routine ACTH test. Whatever the age (1 mo-13 yr), SBP levels decreased significantly (mean=30%) in a group of 40 boys at the end (day 14) of an hCG test (1500 IU/48 h x 7), but the response was very variable and not correlated with testosterone levels. In contrast, the exogenous administration of fluoxymesterone (10 mg/m^2/d.x 10 d.) or depo-testosterone (4 IM injections of 100 mg/m^2 every 2 weeks) induced a siginificant drop (mean 2 fold) in 10 infants with idiopathic male pseudohermaphroditism, but not in 2 suspected of AIS. In conclusion, SBP appears a good marker of androgen sensitivity in infancy, however establishing a protocol requires three conditions: 1) the test should not be done during the 1st month of life (rising basal levels), 2) neither after an ACTH test and 3) utilise the exogenous administration of a high dose of androgens for somewhat a prolonged period of time.

129

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AGE-DEPENDENT EFFECTS OF MELATONIN ADMINISTRATION ON PROSTATIC CYTOSOL ANDROGEN RECEPTORS IN MALE RATS

Chronic daily administration of melatonin (MT) can have potent effects on reproduction in the experimental animals. Various theories have been elaborated to explain these "pineal" effects on gonads. In the present study we have examined the prostatic cytosol androgen receptor (AR) response in pubertal (35-day-old) and adult (70-day-old) male Wistar rats to doses of 250 µg/kg b.w. MT (in 0.5 ml saline) administered s.c. for 4 days at 17.00 hr each day with 12 h (6.00-18.00 h) light per day. The control group received only saline for 4 consecutive days. The animals were sacrificed at 7 a.m. following the last dose. In the pubertal group 6 pools out of 24 animals the mean cytosol AR declined significantly (p=0.03) from a level of 262+120 fmol/mg DNA seen in the control animals to a level of 94.3+119 fmol/mg DNA for the MT-treated group. There was also a decline for the cytosol receptors in the adult group but the difference did not reach significance. Interestingly, the studies again confirmed that perhaps cytosol AR is not dependent on testosterone, as there was no difference in testosterone levels between the control and the experimental groups. Chronic injections of MT for 4 days in adult but not in young animals suppressed circulating MT levels when samples were collected 14 h after last injection. The current study convincingly demonstrates that chronic injections of MT for 4 days in the late light phase of the light-dark cycle have marked inhibitory effects on the prostatic cytosol AR in the pubertal animals but not in the adults as was evidenced earlier in an indirect experiment (Moeller et al. (1983), Res Exp Med 183,157-165).

130

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TRANSIENT OVARIAN TESTOSTERONE AND ANDROSTENEDIONE HYPERSECRETION: A CAUSE OF VIRILISATION OR PREMATURE PUBARCHE IN PREPUBERTAL GIRLS

In two unrelated girls with signs of excessive androgen production,the usual causes (premature adrenarche, mild congenital adrenal hyperplasia, adrenal or ovarian tumor) were excluded. Patient 1 presented at age 3.6 (bone age (BA) 3.75) yrs with hypertrophy (3cm) of the clitoris and erections. Urinary total 17KS (0.7mg/d) and individual steroids (5-pregnenetriol,pregnanetriolone,THS,THDOC,individual 17KS) and plasma DHEA(4.8) and 17OHP(2.7 nmol/l) were normal.Plasma estradiol (E2,142pmol/l) was minimally elevated,but testosterone (T,8.2) and androstenedione (A,10.4nmol /l) were high. At laparotomy, ovarian cysts without evidence of a tumor were found and removed. After surgery, T(0.7) and A(1.6nmol /l)returned to normal and remained so during 5yrs of observation. The clitoris did not change, but erections occurred no longer. Patient 2 presented at 7.8 (BA 9.1) yrs with pubic (stage 2) and axillary hair. Urinary 17KS(1.9 mg/d) and individual steroids, as well as plasma DHEA(7.7),17OHP(3.3nmol/l),and E2(139pmol/l) were normal, but T (7.7) and A (8.1 nmol/l) were elevated. Echography showed polycystic ovaries. Without treatment, T (1.9) and A (2.1 nmol/l)dropped to normal during 3 subsequent yrs, and appropriate puberty started later. Transiently increased ovarian T and A of unknown cause has to be included in the differential diagnosis of excessive androgen production in prepubertal girls.

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