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MINERALOCORTICOIDS (MC) IN THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY (21-OHD). A.N.Tiul'pakov, E.P.Kasatkina and G.V.Ibragimova, Endocrinological Research Center, Institute of Postgraduate Medical Training, Moscow, Russia.

Plasma renin activity (PRA), ACTH, serum 17-OHP, aldosterone (A) and testosterone (T) levels were monitored in 48 children with 21-OHD. There were 37 girls and 11 boys aged from 1.5 months to 14.5 years, 34 salt-losers (SL) and 14 simple-virilizers (SV). Initially, 25/34 SL received glucocorticoids (GC) combined with MC, 9/34 SL and 9/14 SV - only GC, and 5/14 SV - no treatment. To evaluate effect of MC on hormonal control 20/34 SL and 8/14 SV were followed in whom during the study therapy with MC was initiated or intensified, while doses of GC were reduced or not changed. 3-4 weeks after modification of the therapy in these two subgroups both in SL and SV PRA fell from 20.4±3.31 to 2.1±0.49 ($p<0.001$), and from 6.5±3.93 to 3.5±1.33 ng/ml/hr ($p>0.05$), while A decreased from 0.5±0.14 to 0.2±0.11 ($p<0.05$), and from 1.4±0.37 to 0.5±0.21 nmol/l ($p=0.01$), respectively. The inhibition of PRA and A was associated with slight decrease of mean ACTH, 17-OHP, and T, however all these changes were not significant ($p>0.05$). Thus, MC normalize renin-angiotensin system activity in patients with 21-OHD, however their effect on adrenal steroidogenesis may be not so dramatic.

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RANDOMIZED TRIAL OF THE EFFECT OF TWO DIFFERENT PROGESTAGENS ON PLASMA LIPIDS IN GIRLS TREATED FOR TALL STATURE. M. Frambourg, M. Peter, C.-J. Partsch and W.G. Sippell, Division of Paediatric Endocrinology, Dept. of Paediatrics, University of Kiel, Kiel, Germany

In adult women progesterone derivatives have been advocated to be preferable to nortestosterone compounds due to their less negative effects on serum HDL levels. Since comparable data on paediatric patients are lacking, we studied 24 tall girls randomly assigned to either 5 mg of medroxyprogesterone acetate (group A) or 5 mg norethisterone acetate (group B) daily (days 13-23) in addition to 7.5 mg of conjugated estrogens (Presomen) daily. Group A and B did not differ in age and bone age, height, weight, body mass index (BMI), predicted adult height (PAH), plasma cholesterol (4.3 ± 0.9 vs 4.4 ± 0.6 mM; mean ± SD), triglycerides (0.93 ± 0.37 vs 0.75 ± 0.23 mM), HDL- (1.2 ± 0.2 vs 1.3 ± 0.3 mM), LDL-cholesterol (2.6 ± 0.8 vs 2.6 ± 0.6 mM) and HDL/LDL-ratio (0.66 ± 0.41 vs 0.52 ± 0.14). All parameters were followed at 0, 3, 6, 9, 12, 18 months during treatment and 6 mo thereafter. Between and within groups A and B there was no difference/change of any plasma lipid parameter during and after treatment. PAH, near final height and BMI after treatment were comparable in both groups. We conclude, that in contrast to adult women, there is no significant effect of norethisterone on the plasma lipid pattern in young girls treated for tall stature.

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LINKAGE ANALYSES TO ASSIGN THE LOCUS FOR AUTOIMMUNE POLYGLANDULAR DISEASE TYPE I. *J. Perheentupa, J. Aaltonen, J. Komulainen, A. Vikman, A. Palotie, C. Wadelius and L. Peltonen, Children's Hsopital, Helsinki University Central Hospital, Helsinki, Finland and Department of Human Molecular Genetics, National Public Health Institute, Helsinki, Finland*

The autoimmune phenomena associated with many human diseases are still only partially understood. Unravelling the molecular pathogenesis of inherited diseases with a strong autoimmune component in their clinical expression could help to dissect the molecular background of abnormal immune response. One such genetic disorder is autosomal resessive autoimmune polyglandular disease type I (PGD I), also known as autoimmune polyendocrinopathy-candidiasis - ectodermal dystrophy (APECED, MIM 240300). This disease is especially enriched in the genetically isolated population of Finland. Here we have taken advantage of newly developed amplifiable multiallelic microsatellite markers coupled with the microtiter well format of the polymerase chain reaction and linkage analyses to establish the most probable chromosomal location for the APECED locus. The rapid "semiautomated" protocol was here aplied to analyze 100 chromosomally assigned polymorphic loci. The method proved to be an effective and economical tool for gene mapping compared with standard blotting and hybridization and resulted in the preliminary assignment of the APECED locus.

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STRUCTURAL ELEMENTS FOR SPECIFIC BINDING OF ANGIOTENSIN II TO ITS TYPE I RECEPTOR BY SITE-DIRECTED MUTAGENESIS. T. Sano[1], K. Ohyama[1], Y. Yamano[2], M. Ohta[1] and T. Inagami[3], Dept. of Pediatrics, Yamanashi Med. College[1]. Dept. of Agriculture, Tottori University[2]. Dept. of Biochemistry, Vanderbilt University[3]. Yamanashi 409-38, JAPAN[1]

To identify structural components essential for ligand binding in AT_1 receptor, we mutated and transiently expressed the modified rat AT_1 receptors in COS7 cells and examined changes in ligand binding activity. We had already reported that the replacement of any one of 4 Cys with Gly in the extracellular domains markedly reduced the binding affinity. In the present study, we mutated Glu(173) with Gln in the second extracellular loop, and Asp(263) with Asn in the sixth transmembrane domains. The replacement of Asp(263) profundly reduced the binding affinity, but not the maximum binding, whereas the replacement of Glu(173) had a weak effect in the binding affinity. We propose that two extracellular disulfied bridges are essential for the maintenance of active stereo-structure of the receptor, and the charged residue(Asp263) in the sixth transmembrane region is important for the binding of the positive charged structure of angiotensin II.

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ADRENAL FUNCTION AND TYPE III PROCOLLAGEN PROPEPTIDE IN OBESE CHILDREN WITH STRIAE. A.Salvatoni,G. Riganti,G.Gambarini, A.Colombo, A.Meloni,M.P.De Berti,Paediatric Clinic - 2nd Faculty of Medicine and Surgery - University of Pavia - Paediatric Department - "Ospedale di Circolo e Fond. Macchi"- Varese (Italy).

The aim of this study is to establish whether striae in obese children could be considered as a disturbance of adrenal function and/or collagen synthesis and is related to higher risks of developing cardio-vascular disease. We studied 13 obese children with striae and 11 obese children without striae matched for age and weight excess. The patients were classified according to the distribution of the striae in 2 groups: A. limbs or trunk; B. limbs and trunk. In all patients the following parameters were evaluated: height and weight, pubertal stage, weight excess according to the Tanner's Standards, triceps and subscapular skinfolds, waist/hip ratio, systolic and diastolic blood pressure, blood glucose and IRI before and 120' after oral glucose load, BUN, blood uric acid, cholesterol, HDL cholesterol, triglycerides, Apo A1, Apo B, ACTH, DHEA-S, cortisol, estrone and procollagen type III propeptide (PIIIP-RIA), which is a precursor of soft connetive tissue collagen (type III). The caloric and nutrients intake was also evaluated on the basis of a three days alimentary recall.

Group	n	DHEA-S(µg/ml)	ACTH(pg/ml)	Cortisol(ng/ml)	PIIIP(U/ml)	E1(pg/ml)
Striae (mean±SD)	13	1.42±0.65	40±15	119±49	0.96±0.32	79±51
No striae (mean±SD)	11	1.46±0.73	46±18	131±56	1.27±0.47	41±17
p		ns	ns	ns	≤0.05	≤0.025
Group A. (mean±SD)	8	1.49±0.73	42±16	117±50	1.13±0.32	54±29
Group B. (mean±SD)	5	1.30±0.67	35±14	122±59	0.73±0.19	99±64
p		ns	ns	ns	≤0.025	ns

The main results, reported in the table above, suggest that striae in obese children are associated with lower collagen synthesis. Since adrenal function was similar in all groups of patients, the higher estrone blood levels in obese with striae may be due to aromatase activity of fat tissue.

Neuroendocrine, Pituitary

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PEAK GH RESPONSE TO VARIOUS PROVOCATIVE STIMULI IN CHILDREN WITH NORMAL AND FAMILIAL SHORT STATURE.

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The reliability of provocative stimuli of GH secretion in the diagnosis of GH deficiency it is still unclear. Until now normative values of GH response to various stimuli are scanty. To address this point, in a very large population of children with normal and familial short stature (n=432; 282 M and 150 F; age 10.6±0.7 yrs; pubertal stage I-III) having normal spontaneous GH secretion and IGF-I levels, we studied the GH response to: a) physical exercise (PE; n=23); b) insulin-induced hypoglycemia (IH; n=44; 0.1 U/kg regular insulin iv at 0 min); c) arginine (ARG; n=65; 0.5 g/kg iv from 0 to 30 min); d) clonidine (CLON; n=86; 150 µg orally at 0 min); e) L-DOPA (n=37; 125, 250 and 500 mg orally for body weight <15, between 15 and 30, and >30 kg, respectively); f) glucagon (GLU; n=40; 1 mg im at 0 min); g) pyridostigmine (PD; n=51; 60 mg orally at 0 min); h) GHRH (n=94; 1 µg/kg iv a 0 min); i) PD + GHRH (n=84; PD given 60 min before GHRH); l) ARG + GHRH (n=69; GHRH at 0 min and ARG from 0 to 30 min). The mean (± SEM) peaks and ranges of GH responses to various stimuli were: a): PE: 12.2±1.3 µg/L; 3-28.3; b) IH: 13.4±1.5 µg/L; 2.7-46.4; c) ARG: 16.7±1.3 µg/L; 4.3-48.4; d) CLON: 18.1±1.4 µg/L; 3.8-86; e) L-DOPA: 13.9±1.6 µg/L; 1.9-40. f) GLU: 16.6±1.8 µg/L; 1.9-49.5; g) PD: 13.6±1.0 µg/L; 2.5-35; h) GHRH: 33.4±2.6 µg/L; 2.8-102.7; i) PD + GHRH: 47.5±1.8 µg/L; 19.6-92; l) ARG+GHRH: 62.1±2.8 µg/L; 20.4-107.0. The lower limit at 97% of confidence interval for various stimuli was: a)PE: 3.0; b)IH: 4.0; c)ARG: 4.4; d)CLON: 4.7; e)L-DOPA: 2.4; f)GLU: 3.1; g)PD:3.1; h)GHRH: 6.2; i)PD+GHRH: 22; l)ARG+GHRH: 27.3. Thus, in conclusion, our data show that all conventional stimuli of GH secretion such as PE, IH, ARG, CLON, L-DOPA, GLU as well as PD alone and GHRH alone have very low limits of normal peak GH response. These limits are lower than those classically indicated as 7 or 10 µg/L. When combined with PD or ARG, GHRH becomes the most powerful single test to explore the integrity of somatotroph cells. The lower limit of normal peak GH response to testing with GHRH combined with PD or ARG is over 20 µg/L. The availability of tests having an elevated lower limit of normality allows to better differentiate between normal and impaired pituitary function, thought a normal GH response to these tests does not rule out the existence of a hyposecretory state due to hypothalamic dysfunction.