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Role of androgens in male pseudohermaphroditism.

Studies in a large Arab kindred revealed 23 male pseudohermaphrodites due to 17 β-hydroxysteroid dehydrogenase deficiency. All individuals were reared as females even though their external genitalia were mild to moderately ambiguous at birth. At puberty, male body habitus with normal secondary sexual characteristics developed. Gynecomastia was absent. The phallus and testes enlarged to adult proportions and a spontaneous change to male gender role occured in several individuals. The biochemical defect was demonstrable only after puberty and consisted of greatly elevated Δ4-androstenedione (300-1300 ng/dl) with relatively low testosterone levels (0.7-3 ng/ml). Dehydroepiandrosterone levels were either normal or moderately elevated while 17 β-estradiol was elevated (36-130 pg/ml). LH and FSH levels were very high post-puberty, but normal before. However, there was overresponse to LHRH in all age groups.

It is difficult to explain the development of the male phenotype with change of gender identity and role solely on the basis of the relatively low testosterone levels. Therefore, it is conceivable that the very high Δ4-androstenedione levels play a major role in this respect.

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Menarche and subsequent ovarian function in girls with congenital adrenal hyperplasia (CAH).

Chronological age, body weight and plasma steroid concentrations at menarche, and subsequent ovarian function in relation to plasma/saliva steroid concentrations and glucocorticoid therapy were reviewed in 6 girls with 21-hydroxylase deficiency (3 salt-losers). Mean age at menarche was 13.6 yr (12.6-14.5); body weight varied from 45 to 66 kg. Menarche did not occur with plasma testosterone (T) levels of 5-6 nmol/L. Normal female plasma T levels occurred on changing from hydrocortisone to single dose dexamethasone (dex) given as 0.25 to 0.75 mg/day. The potency of dex relative to cortisol was 80:1 based on adrenal suppression effect. Regular menses occurred with plasma T levels in the normal female range. Ovulatory cycles were documented using menstrual profiles of saliva progesterone (P) performed at a post-menarchal age of 3.0-3.4 yr. Some showed the characteristic rise in luteal levels of saliva 17P indicating previous ovulation; one 16 yr old girl became pregnant. Anovulatory cycles also occurred in well-controlled girls. Preliminary data on controls showed absence of ovulatory cycles for at least 2 yr post-menarche. Conclusions: in CAH, 1) Menarche is not usually delayed. 2) Ovulatory cycles may be delayed but further control data is needed. 3) Normal plasma T levels are required for regular menses. 4) This can be achieved using single dose dex. therapy.

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Dissociation of cortisol and adrenal androgens (AA) in selected patients with hypopituitarism.

Dissociation of secretion of cortisol and AA, observed in several physiologic and pathologic conditions, has led to the hypothesis that secretion of AA may be controlled by another hormone in addition to ACTH. An alternate hypothesis attempts to explain all instances of such dissociation by changes in ACTH alone, wherein ACTH controls synthesis of AA by changing the intraadrenal concentration of cortisol. This hypothesis does not allow for dissociation of cortisol and AA in a subject with normal ACTH secretion and intact adrenals. To test this hypothesis, we studied cortisol secretion in 4 patients (20-26 years) with idiopathic hypopituitarism (who never received cortisol replacement therapy) and deficiency of AA as reflected by lack of adrenarche and low levels of serum DHEAS. Determination of serum cortisol and 17-OH progesterone (17 OHP) at 2 h intervals for 2 days and of cortisol and 17 OHP responses to insulin induced hypoglycemia and glucagon infusion revealed normal cortisol and 17 OHP secretion in 2 of the 4 patients. Although intraadrenal concentrations of cortisol and serum levels of ACTH were not measured, there is no reason to suspect that these levels should be abnormal in the 2 patients who had normal cortisol secretion. Low serum levels of DHEAS in these patients cannot be explained by deficiency of ACTH secretion. Our data provide further evidence that secretion of AA may be controlled by another hormone in addition to ACTH.

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DIFFERENTIATION OF PSEUDOHYPOALDOSTERONISM (PHA) AND ADRENAL BIOSYNTHETIC DEFECTS.

Adrenal salt-wasting diseases in the neonatal period and early infancy can be confirmed by the pattern of steroids excreted in urine. The presence or absence of cortisol, aldosterone and corticosterone metabolites, plus certain precursors, is established in a single analysis of steroids using gas chromatography with capillary columns and mass spectrometry.

In infants (n=5) with the Type II biosynthetic defect of aldosterone, the excretion of corticosterone and 18-hydroxycorticosterone metabolites were elevated. In PHA (n=8), both 18-hydroxycorticosterone and aldosterone metabolites were found at high concentrations in urine. When salt loss was controlled by replacement therapy or sodium supplements respectively, and plasma renin activity (pRA) were normalised, the excretion rates of the metabolites were lower but the ratios of excretion for 18-hydroxycorticosterone to aldosterone metabolites were greater than 30 to 1 in the biosynthetic defect but nearer unity in PHA. The interpretation of the overall pattern of steroid excretion also requires consideration of the changes in the nature of steroid metabolites in newborns through infancy, since conjugates of tetrahydro-metabolites replace hydroxylated and free compounds. These studies are complementary to determinations of pRA and plasma steroid concentrations in defining the diagnosis of infantile salt wasting disease.

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Insulin receptors in the live rat fetus. Differential effects of maturation according to cellular type.

Purified carrier-free monoiodinated insulin (Ins*) alone or mixed with an excess of native insulin was injected into the vitelline vein of 17, 19 or 21 day-post coitum (d.p.c.) rat fetuses in utero. Several organs concentrated Ins* among which liver, kidneys, heart, jejuno-ileum and lungs. Their radioactivity was analyzed by gel chromatography and autohistoradiography. In the 3 age groups, the liver had the highest specific activity: binding was saturable, partly reversible, associated with the hepatocytes and to a lower extent with the liver hematopoietic cells. Liver maturation was essentially characterized by a progressively increasing rate of hormone internalization and degradation. In the lungs, high affinity and saturable binding was associated with the glycogen-laden cells of the bronchial tubes (pseudoglandular stage: 17 d.p.c. fetuses). Ins* binding was no longer observed in more mature surfactant synthetizing cells (canalicular, 19 d.p.c. and alveolar, 21 d.p.c. stages).
In conclusion: 1. Insulin receptors ontogenesis occurs early in gestation. 2. During the last 5 days of intra-uterine life, cytodifferentiation differently affects insulin metabolism at the cellular level, inducing loss of insulin receptors (lungs) or maturation of post receptor steps (hepatocytes).

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In vivo insulin sensitivity and insulin binding to erythrocytes in children.

The aim of this study was to determine whether RBC insulin receptor assay represents an useful means for assessment of the clinical sensitivity of insulin. Steady State Plasma Glucose (SSPG) was established by constant infusion of somatostatin (125μg loading followed by 125μg/m²/hr), glucose (6mg/kg/min) and insulin (0.8 mU/kg/min). Insulin binding to RBC receptors was measured and compared with SSPG. Insulin binding to RBC was assayed by the modified method of Gambhir. Plasma insulin area was measured by GTT. A decreased specific insulin binding (SB) to RBC, due to reduced receptor concentrations was observed in hyperinsulinemic obese children. In 21 children with various body weights, SB was inversely related to fasting plasma insulin level ($r=-0.651$, $p<0.01$) and also with plasma insulin area ($r=-0.547$, $p<0.01$). A highly significant inversed correlation was noted between SSPG and SB ($r=-0.807$, $p<0.005$). SSPG was, also, correlated with the fasting plasma insulin level ($r=0.669$, $p<0.05$). It was concluded that RBC insulin receptor is an useful tool for clinical evaluation of tissue insulin sensitivity.