28 E. MALLET*, Ph. BRUNELLE, P. CARAYON, Th. DUCASTELLE (Intr. by M.C. Postel-Vinay). Thyroïd dysfunction in pseudohypoparathyroïdism : evidence for a coupling failure of the thyrotropin receptor adenylate cyclase system associated with morphological abnormalities of the thyroïd follicles. Département de Pédiatrie, Hôpital Ch. Nicolle, 76031 ROUEN, FRANCE

A case of pseudohypoparathyroïdism type I in a 17 years old female coexisting with thyroïd dysfunction meeting all the criteria for thyrotropin (TSH) insensitivity is studied. Thyroïd gland was not enlarged as confirmed by scintiscan. Laboratory findings included : high basal concentration of TSH (17-19.2 µU/ml), normal values of circulating thyroïd hormones (T_4 : 6.3 µg/ml, T_3 : 98 ng/ml) exagerated response of TSH to thyrotropin releasing hormone (TRH) (200 µg) and low 131 I thyroïd uptake with impaired response to exogenous TSH (bovine TSH 10 UI daily for 6 days). After T_3 therapy (50 µg per day for 2 months), serum TSH decreased to the normal range and its response to TRH almost normalize. Tests for circulating thyroïd antibodies were negative. Light microscopy of a biopsy specimen showed a heterogenous cellular activity with large follicles with abundant colloïd and flattened lining cells. The electron microscopy showed deep infoldings of the basal membrane. The TSH receptor as well as the basal and NaF stimulated adenylate cyclase (AC) of thyroïd membranes were found to be normal, but the ability of TSH to stimulate AC was markedly decreased suggesting a coupling abnormality between the TSH receptor and AC. This abnormality could cause the resistance of target organs in pseudohypoparathyroïdism to parathyroïd hormone.

29 F. BIDLINGMAIER and D. KNORR, Children's Hospital, University of Munich, Germany. Development of the negative feedback control system of the hypothalamo-pituitary-gonadal (HPG) axis in the male rat fetus.

To evaluate the development of the HPG axis the method of immunologic hormone inactivation was used to study male rat fetuses at different ages of gestation. From the 12th day of gestation pregnant rats were passively immunized against testosterone (T) by daily injections of rabbit antiserum with high binding capacity for T. Fetuses were studied on each day of gestation starting at day 18. Antibodies against T were detected in all fetal plasma samples. While the reduction of circulating free T by antibody binding did not affect the differentiation of the male genital tract it markedly stimulated the endocrine activity of the testes. At day 19 and all subsequent days of gestation the testicular T content -an index of circulating gonadotropins- was significantly higher in immunized fetuses than in controls. However, this difference was not yet apparent at day 18 when the normal fetal rat testis shows its peak activity. These results indicate that in the male rat fetus the negative feedback between gonads and hypothalamo-pituitary system develops between day 18 and 19 of gestation when the differentiation of the genital tract is already well advanced.

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Down-regulation of gonadotropin release by the ovine fetal pituitary gland by the superagonist D-Trp^6Pro^9NET-LRF.

D-Trp^6Pro^9NET-LRF (Trp^6-LRF) a superagonist analogue of LRF has caused suppression of gonadotropin secretion when administered chronically in animals and in humans, but has not been studied in the fetus. In 3 chronically catheterized ovine fetuses ages 105-130 days (term 147±3), spontaneous LH pulses of 3-8 ng/ml occurred every 3-4 hrs with baseline levels of less than 1 ng/ml. FSH levels ranged from 4-8 ng/ml and did not vary with the LH discharge. Administration of 5 µg synthetic LRF IV produced a mean incremental increase (Δ) of LH of 6.8 ng/ml (range 5.8-7.7 ng/ml), while the mean Δ of FSH was 1.9 ng/ml (0.9-2.9 ng/ml). After the first 10 µg dose of Trp^6-LRF IV, the mean Δ of LH was 16.4 ng/ml (4.9-25.6 ng/ml), and the mean Δ of FSH was 3.9 ng/ml (2.9-4.7 ng/ml). Elevated levels of LH and FSH were sustained for 2 hrs after the agonist. A second 10 µg dose given 24 hrs later did not induce a significant rise in LH or FSH. Intravenous LRF elicited a minimal rise in LH and FSH during a 2-14 day study period, without measurable LH pulses. The findings are consistent with an initial phase in which Trp^6-LRF stimulates FSH and LH release followed by a prolonged phase of refractoriness to either LRF or the LRF agonist. The later effect is consistent with down-regulation of fetal pituitary LRF receptors. These observations provide further support for the influence of endogenous fetal LRF on fetal gonadotropin secretion and of neuroendocrine control mediated by LRF as early as 105 days of gestation.

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Human Fetal Adrenal Cell Responses to ACTH and Pituitary Extracts.

Human fetal adrenal tissues were studied in dispersed cell suspensions prepared by collagenase digestion;triplicate aliquots were incubated for 2 hours; control cells were compared to cells stimulated with 3 dilutions of ACTH and compared to responses from cells stimulated with 3 dilutions of 2 fractions prepared from human pituitaries ("A" and "B"). Crude fraction A contained FSH, LH and TSH; B contained ACTH, MSH and other peptides. 4 specimens with single adrenal weights of 128 mg, 243 mg, 488 mg and 915 mg were studied. Incubation medium was analyzed for dehydroepiandrosterone sulfate (DHAS) and corticoids (C). Unstimulated C secretion was similar in all weights (137 ± 63 pg/ml/100,000 cells); DHAS secretion was variable but increased with increasing size (16 ng/ml to 56 ng/ml/100,000 cells). ACTH caused dose-related proportionate increases in both DHAS and C in all; pit. frx "A" gave greater DHAS responses than ACTH in the 243 mg adrenal: DHAS:C ratio of 233:1 for ACTH and 7051:1 for "A." However, this was not found in the more mature 915 mg gland (311:1 for ACTH and 191:1 for "A"). "B" reacted like ACTH. We conclude that (a) the developing fetal adrenal shows changing responses to different stimuli, perhaps reflecting changes in receptor response, number or discrimination, and (b) pituitary extract "A" may contain an androgen stimulator effective at variable stages of development.

32 J.W. REYNOLDS AND C.V. CARLSON* Dept of Pediatrics, Univ of Oregon Health Sciences Center, Portland, OR, USA.

Fetoplacental Steroid Metabolism in Prolonged Pregnancy and Postmaturity Syndrome.

Previous work from this laboratory (Pediat. Res. 14:1367, 1980) showed that post-term infants (>42 wk. gestation) with postmaturity syndrome had normal umbilical venous dehydroepiandrosterone sulfate (DHAS) levels, but low unconjugated estriol (E_3) levels, as compared to post-term infants with no evidence of dysmaturity. To investigate further whether placental conversion of neutral steroids to estrogens is more limiting for E_3 production than fetal adrenal DHAS secretion, we studied 14 women with prolonged prognancy (>42 wk) and 9 control 39-41 wk gestation women by 50 mg I.V. DHAS infusions 1-3 days before delivery. The DHAS $T_{½}$ was longer in post-term pregnancies than in controls (3.46 ± 1.13 hr vs. 2.79 ± 1.05 hr, $p < 0.01$), and the estrone (E_1) increases at 2 and 3 hr., and estradiol-17β (E_2) increases at 2 and 4 hr. ($p<0.05$) were less in post-term than control pregnancies. These findings indicate diminished placental aromatizing function in prolonged pregnancy. However, no differences between pregnancies with and without post-mature fetuses could be found. In contrast, E_1, E_2 and DHAS levels in umbilical venous blood levels were similar, and E_3 levels were lower ($p<0.05$), in postmature newborns when compared to controls. These cord blood values indicate that fetal hepatic 16α-hydroxylase may be the limiting step in fetoplacental E_3 production in some postmature fetuses.

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Defective up-regulation of androgen-receptor activity: a new marker of androgen resistance (AR) in man.

An infant (#99) with ambiguous genitalia was investigated for androgen resistance. Foreskin-derived fibroblasts were normal in respect of: 5α-reductase activity (23 pmol/mg protein/hr); receptor concentration (25 fmol/mg protein); dissociation constant (K_d=0.25 nM); dissociation rate ($k_{-1}=6\times10^{-3}min^{-1}$)of the whole cell DHT-receptor "activity" at 37°C; and thermostability at 42°C.However, preincubation of the fibroblasts from #99 with 3-10 nM DHT for up to 20h (37°C) caused no increase in receptor activity (n=5). In contrast, normal fibroblasts doubled their activity (range of 20h/1h values =1.7-2.8, n=20). This increase is suppressed by 2 µM cycloheximide, and is likely to be a form of "up-regulation" reflecting a larger pool of receptor molecules. A similar up-regulation defect has been observed in another patient with partial AR** in whom the activity showed thermolability and a three-fold greater than normal k_{-1}. The isolated expression of a regulatory defect in #99 indicates: (i) that it is functionally separate from the accompanying thermal and dissociative defects in the other patient; (ii) that 99's mutation probably affected a domain of the androgen receptor molecule that normally acts as the signal for up-regulation.

** Pediatr Res 14 (4,part 2), 483,1980