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hCG-induced steroidogenic refractoriness of Leydig cells : I. Experimental evidence of receptor and post-receptor modulation of gonadotropin action.

In intact male rats (IMR) a single injection of hCG (10-500 IU) induced a peak of plasma testosterone (T) 2 hrs later. Plasma T decrease thereafter in spite of high levels of hCG, indicating steroidogenic refractoriness to hCG stimulation. Leydig cells isolated from testis of hCG treated rats were insensitive to *in vitro* stimulation by hCG, cholera toxin and dibutyryl cAMP. In addition a decrease in the number of hCG binding sites appears some hours later than refractoriness. Responsiveness to hCG was restaured 4 to 5 days after hCG injection. In hypophysectomized (Hpx) rats the early T response was 20 times lower than in IMR. However hCG induced the same refractoriness than in IMR, while at the end of this period T response to hCG was similar to that of IMR. It is concluded that hCG induced refractoriness is related to three phenomena : modification of the coupling between the hCG binding site and adenylate cyclase, abnormality of some step beyond cAMP formation and decrease of the hCG binding sites. In addition, in Hpx rats a "maturation" of the steroidogenic pathways occurs during the refractoriness period.

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hCG-induced steroidogenic refractoriness of Leydig cells : II. In vivo studies in human.

Male adult volunteers were given 6000 IU of hCG IV x 2 at 24 hours interval and plasma levels of Testosterone (T) measured at various times for one week. Prepubertal boys received 7 IM injections of 1500 IU of hCG every other day for clinical purposes and blood obtained before hCG and 4 hours after each injection. In adults T increased after the first hCG injection, peaked 2-4 hrs later, but decreased almost to basal levels within 24 hrs. The 2nd hCG injection was unable to increase significantly T levels ; however (without any further hCG injection) an important rebound in T levels was observed 3 to 4 days later. In children a progressive increase in T levels was observed throughout the 2 weeks of hCG stimulation. Thus the pattern of response to hCG stimulation observed in adult men reproduces the one observed in intact adult rats while that observed in prepubertal children evokes the one observed in hypophysectomized rats (cf. preceding abstract). It is concluded that 1) the phenomenon of hCG-induced steroidogenic refractoriness as demonstrated in the rat occurs in adult men. 2) this phenomenon is only observed when significant levels of endogenous LH are present. 3) in adult men daily injections of hCG are not an adequate protocole to study Leydig cell function.

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Evidence of the importance of testosterone (T) for the control of the fetal hypothalamo-pituitary-gonadal (HPG) system in rabbits.

Recently we have demonstrated inhibition of masculine differentiation in male offspring of female rabbits actively immunised against T. After passage through the placenta the T-antibodies not only inhibit the entry of T into the fetal target cells but also protect it from metabolism. Thus, besides marked feminisation, 1000-fold elevated plasma T levels in the male fetuses are observed. To assess the influence of T-antibodies on fetal testes we studied histologically the testes of 7 neonates born by 3 T-immunised rabbits and of 3 controls. No influence on testicular differentiation could be observed. However, the neonates immunologically deprived of T showed significantly enlarged interstitium and the number of Leydig cells was twice as high as in the controls. These findings indicate increased stimulation of the testes in these animals and suggest that normally even in the fetus a negative feedback is acting between testes and hypothalamo-pituitary system, which is interrupted by T-antibodies. Obviously T plays an important role in the control of the HPG system in the male fetus.

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Endocrine studies in boys with pubertal gynecomastia.

25 XY boys aged 13 to 19 years with pubertal gynecomastia (breast development $>$ 6 cm) were studied. According to their pubertal development, they were classified as 7 P2, 9 P3, 7 P4 and 2 P5. Results were compared to those established in normal boys at equivalent pubertal stages. The data demonstrated significantly increased plasma levels of testosterone (T) at stages P2 and 3 ($p<0.001$) and P4 ($p<0.05$), post HCG (3x1500 u) T at stage P2 ($p<0.005$), T-estradiol binding globulin at stage P2 ($p<0.005$), estrone and estradiol at stages P2 and 3 ($p<0.005$). Plasma prolactin levels and LH and FSH responses to LHRH were normal in all cases. The most striking fact is the overproduction of testosterone in the initial steps of puberty contrasting with the degree of virilization, the development of breast and the lack of decrease of TeBG. These data suggest a transient peripheral unresponsiveness to testosterone with subsequent conversion in estrogens.

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Pubertal gynecomastia: Evidence for a possible role of the adrenal gland.

As part of a longitudinal study of normal puberty, 14 boys who developed gynecomastia and 6 normal boys were followed at 6 month intervals from age 11 to 17 years. Serum levels of E_1, E_2, Δ_4, T, DHEA, DHEA-S and PRL were measured at each interval. Mean age at onset of gynecomastia was 14.0±0.28 years, mean bone age 13.0±0.26 years and mean pubertal stage 2.9±0.13. Over the course of puberty there were no significant differences in mean levels of these hormones. However, ratios of E_1/Δ_4, E_1/DHEA and E_1/DHEA-S were consistently higher in the gynecomastia group between ages 12½ and 15 years. The same tendency was noted for these ratios for bone age years 12½ to 15 and pubertal stages 2 through 4. Conversely the ratio of E_2/T remained essentially the same between the two groups. These results suggest that either adrenal secretions or increased peripheral conversion of Δ_4 to E_1 may play a role in the appearance of pubertal gynecomastia in normal boys.

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Reduced early postnatal rise of plasma testosterone in cryptorchidism.

Plasma T was measured from 10 to 120 days in 29 full-term males born with undescended testes (14) or testis (15). At 4 months 16 remained cryptorchid (group A) while spontaneous descent occurred in 13 (group B). 49 plasma samples from these patients were compared to 45 controls (C). The postnatal T rise was significantly (*$p<0.05$, **$p<0.01$) reduced from 10 to 89 days in group A compared to B and to C, T (ng/ml, mean ± SEM) levels being : 10-29 days A 0.51±0.16**, B 2.87±0.41, C 2.00±0.21 ; 30-59 days A 1.23±0.70*, B 3.46±0.55, C 3.08±0.58 ; 60-89 days A 1.13±0.27**, B 4.27±0.44, C 2.81±1.06 ; 90-120 days A 0.38±0.20, C 1.42±0.41. No difference was found between uni and bilateral cases in groups A and B. It is concluded that early Leydig cell secretion is impaired in cryptorchidism and normal in delayed testicular descent, thus suggesting that testosterone deficiency may play a role in the defect of testicular descent and maturation in true cryptorchids.