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Testosterone (T) decrease after ACTH : a glucocorticoid mediated process.

In a previous report (ESPE 1977, abst. 67) it was shown that in boys at pubertal stage (P) 2, T levels were significantly reduced by dexamethasone (DXM). As T production at P2 may be both from adrenal and gonadal sources, the significance of this inhibition was further investigated in advanced pubertal stages.

20 boys at P2 and 15 boys at P3-4 were studied after informed consent of parents. At P2, T morning levels ($\bar{x}$ ± sem) before DXM, after 1 mg DXM given at 9 p.m. and 60 mn after Synacthen 250 µg /m^2, were respectively in nmol/l : 2.7 ± 0.46, 1.5 ± 0.27, 1.5 ± 0.31 ($p < 0.002$). At P3-4 T levels were reduced by DXM from 9.8 ± 1.1 to 6.6 ± 1.0 ($p < 0.01$) and further reduced after Synacthen up to 4.9 ± 0.9 ($p = 0.02$). In nine adult male volunteers morning T levels were reduced from 21 ± 1.7 to 18 ± 1.7 ($p = 0.05$) by DXM (3 mg x 3 days). 5000 IU hCG given intramuscularly under DXM treatment induced a response not differing from control group (34 ± 1.7, 30 ± 2.1, $p > 0.10$). These findings support the conception that ACTH induced inhibition of T production is mediated by glucocorticoids. The effect of DXM seems to be dose-related since in boys with larger body size (P3-4), Synacthen induced a further decrease of T, but not in boys at P2 where inhibition is maximal with the same DXM dosage. The unaltered responsiveness to hCG in adult does not support an inhibitory effect of DXM upon LH action on Leydig cells.

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Studies of the 17-desoxy, 17-hydroxy, and C_{19} androgens in conjunction with congenital adrenal hyperplasia (21-OH deficiency).

Hormonal response to 6 hour ACTH stimulation was determined in 24 sibs predicted to be heterozygous carriers of the gene for 21-OH-def. by HLA genotyping and 14 parents, obligate heterozygotes. Confirming the findings of Grosse-Wilde, et al (Immunogenetics, 8:41, 1979) in pre-pubertal children and post-pubertal males predicted to be heterozygous carriers of the gene based on HLA genotyping, the mean 17-OH-P levels (13, 17 ng/ml respectively) were significantly higher (p<.001) than in the control children and adults (3.9, 5.3 ng/ml respectively). In post-menarchal females the mean 17-OH-P response in the heterozygotes (12.1 ng/ml) was significantly higher (p<.005) than in the general population (5.2 ng/ml); however the overlapping values did not permit a clear differentiation of the hormonal responses in these two groups. Plasma ACTH levels and all other ACTH stimulated steroids including 17-OH pregnenolone, 11-desoxycortisol, cortisol, progesterone, DOC, B, aldosterone, Δ-4-androstenedione, dehydroepiandrosterone, and testosterone whether analyzed alone or in combination did not discriminate between the control population and the heterozygotes. In summary, in sibs predicted to be heterozygous by HLA genotyping and obligate heterozygote parents, mild 21 hydroxlase deficiency was expressed in the 17 hydroxy pathway but was not evident in the 17-desoxy pathway or C_{19} androgens after ACTH stimulation.

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Location of the gene for 21-hydroxylase deficiency

We have studied 34 families in whom the propositus had CAH and confirm the original observation (1) that the gene responsible is closely related to the HLA loci. In one family the paternal HLA antigens were A1 B8, B37, DRW5 and the maternal antigens A3, A9, CW3, CW5 B12, B40, DRW1, DRW5. Two affected daughters had A1, A3, CW3, B8, B40, DRW1, DRW5 and A1, A3, CW3, B8, B40, DRW5. From these results we deduce the haplotypes of the family to be: father A1, B8, DRW5/A1, B37, DRW5; mother A3, CW3, B40, DRW1/A9, CW5, B12, DRW5; first daughter A1, B8, DRW5/A3, CW3, B40, DRW1; second daughter A1, B8, DRW5/A3, CW3, B40, DRW5. These findings are explicable on the basis of recombination between the B and DR loci in the mother. Earlier work (2) had located the gene responsible for 21-hydroxylase deficiency to lie between locus A and the GLO locus. CONCLUSION: The present results narrow the locus of the 21-hydroxylase deficiency gene to between the A and DR loci of the major histocompatibility region on chromosome 6.

1. Dupont, B. et al. Lancet, 1977, 2, 1309.

2. Levine, L.S. et al. New Engl J Med. 1978, 299, 911

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Linkage between HLA antigens and obesity.

We performed HLA typing in 122 obese children, 47 with a history of familial obesity and 75 with a negative history. The control group consisted of 905 subjects, without family relation with patients, living in the same geographical area. Our results show: 1)in the 47 patients with familial obesity a significant increase in HLA B13 antigen as compared to controls ($p < .05$), with a relative risk of 3.45; 2)in the 75 patients without a history of familial obesity a significant fall in HLA A2 antigen ($p < .03$) as compared to controls. 3)All obese patients evidenced a highly significant increase in HLA -A and -B blanks as compared to controls, the increase being higher for locus A (chi square=47.83, $p \ll .0001$) than for locus B (chi square=9.20, $p < .003$). This seems to support the hypothesis that at least in a number of patients hereditary predisposition plays an important role in the aetiology of obesity and to indicate that such predisposition involves genes controlled by the HLA chromosomic region. The higher frequency of blanks in obese subjects might be connected with a diminished phenotypic expression of HLA antigens or with the presence in the serum of obese patients of a HLA antigens masking factor.

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Parathormone and calcitonin in the pathogenesis of neonatal hypocalcemia.

Hypocalcemia (HOC) is common in infants of diabetic mothers (IDM), premature newborns (NB), and asphyxiated infants. In addition, it is more frequent in boys than in girls. To investigate the cause of HOC, we have measured serum calcium, RIA-parathormone (PTH), and calcitonin (CT) in IDM, premature, and asphyxiated NB during the first week of life. These subjects were compared to healthy term infants as well as a group of neonates with documented HOC ($Ca \leq 7.5$ mg/dl). Mean PTH and CT concentrations were similar in both sexes and in vaginal (n=188) and cesarean section deliveries (124), and there was no difference between small (18), appropriate (144), and large (42) for date term NB. Serum PTH in premature NB, however, was significantly lower ($p<0.05$) and CT concentrations were higher ($p<0.01$) than in term NB. IDM had low PTH levels ($p<0.05$), but CT concentrations were not different from controls. Asphyxiated infants had both, elevated PTH and CT levels ($p<0.01$). Mean PTH concentrations in hypocalcemic NB were not different from controls, but CT levels were higher than in any other infant group ($p<0.001$). These data suggest that hypercalcitoninemia and hypoparathyroidism alone may cause HOC, but that the risk of HOC is particularly high in infants with combined hypoparathyroidism and hypercalcitoninemia.

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Effect of glucose deprivation on sulfatide synthesis in dissociated brain cell cultures of newborn mice.

Sulfatide synthesis (SFS) in brain cells is a marker for cell differentiation. SFS was measured by incorporation of $^{35}SO_4$ into sulfatide in cultured brain cells of newborn mice at 13 days in culture after exposure to various glucose concentrations for the preceding 72hrs. This age range corresponds to an in vivo developmental stage of rapid myelination. Glucose extraction from the medium during the first 24hrs was independent from the initial glucose level down to 1mM. Thus the duration of severe glucose deficiency (below 1mM) was related to the initial glucose supply. SFS was progressively reduced with increasing duration of severe glucose deprivation reaching 3.5% of controls after 48hrs of glucose deficiency. In the cell homogenates the sulfatide synthetizing enzyme cerebroside sulfotransferase was similarly reduced following glucose depletion keeping a residual activity of 10%. This indicates that a lack of precursors or substrates was not the only cause of SFS reduction. Replenishment of glucose stores in the medium after a starvation period of 14hrs only failed to recover SFS. Reexposure of glucose deprived cells to glucose even led to a further decrease of SFS suggesting a possible toxic effect of glucose on brain cells previously damaged by glucose depletion.