

11 RELATIONSHIP BETWEEN ADRENAL STEROIDS AND GONADOTROPHINS IN PUBERTAL DEVELOPMENT.

J. R. Ducharme, R. Collu, J. Letarte and G. Leboeuf
Laboratoire d'Endocrinologie et Métabolisme and Département de Pédiatrie, l'Université de Montréal and l'Hôpital Sainte-Justine, Montréal, Québec, Canada.

The mechanisms which lead to the activation of the hypothalamopituitary gonadal axis at puberty remain speculative. It is generally accepted that a change in sensitivity of the hypothalamus to feedback effect of circulating sex hormones occurs in the early phases of sexual maturation. Last year, Ducharme et al have presented at this society suggestive evidence that some adrenal steroids may play a role in elevating the gonadostatic threshold to circulating androgens and estrogens at this period. In order to study this interrelationship further, plasma Testosterone (T), Androstenedione (Δ), Estrone (E_1), Estradiol (E_2) were measured by radioimmunoassay at different stages of sexual development and correlated with plasma HGH and HFSH. In addition, the response to LH/FSH-RH was evaluated in precocious and delayed puberty. An elevation of Δ and E_1 , preceded any increase in gonadotrophins which in turn preceded the expected increase in T and E_2 . A parallel displacement in this time sequence relationship was noted in subjects with precocious or delayed puberty. The pattern of gonadotrophins response to LH/FSH-RH correlated better with plasma levels of "adrenal" than "gonadal" steroids. These studies bring additional confirmatory evidence that adrenal steroids may play an important role in the early hypothalamo-pituitary regulatory changes characteristic of puberty.

12 VARIOUS TYPES OF PITUITARY RESPONSE TO THYROTROPIN RELEASING HORMONE (TRH) IN HYPOPHYSECTOMIZED PATIENTS.

J.L. Chaussain, E. Binet, J. Vassal and J.C. Job.
Hôpital Saint-Vincent-de-Paul, Paris, France.

In normal children, TRH injection is followed by a constant significant rise of serum TSH. In view to investigate the hypothalamo-pituitary-thyroid axis in hypopituitarism, 200 $\mu\text{g}/\text{m}^2$ of synthetic TRH were venously injected in children and adolescents with tumoral (n = 24) or idiopathic (n = 29) hypopituitarism.

In 26 patients with normal plasma T_4 , TRH induced 18 times a rise of serum TSH from 5.9 to a mean peak value of 18.2 $\mu\text{U}/\text{ml}$, similar to controls. However in 8, TSH failed to rise after TRH suggesting a peculiar type of hypothalamic deficiency.

12 hypopituitary patients with low T_4 (6 idiopathic, 6 tumoral) had undetectable basal serum TSH and a prolonged rise after TRH with a peak value similar to that of controls (17.4 $\mu\text{U}/\text{ml}$), demonstrating a primary hypothalamic deficiency. 7 others, who had also undetectable basal TSH levels failed to respond to TRH, demonstrating a primitive pituitary failure.

In 4 others (2 tumoral, 2 idiopathic) with multiple deficiencies and low T_4 , the response to TRH was exaggerated, suggesting a tertiary associated hypothyroidism.

In 4 hypopituitary children with low plasma T_4 (3 idiopathic, 1 tumoral), TSH basal levels were definitely elevated and failed to rise after TRH. Anti-TSH antibodies were demonstrated in their sera.

These data demonstrate further that TRH test is a most valuable tool in the study of children with hypopituitarism leading to detection of different kinds of deficiency.

13 ELEVATED BASAL PLASMA TSH IN CHILDREN WITH GROWTH HORMONE (GH) DEFICIENCY AND HYPOTHALAMIC HYPOTHYROIDISM. Helena Krawczynska,

Ruth Illig and Andrea Prader. Univ. Zürich, Sch. Med., Dept. Ped., Kinderspital, Zürich, Switzerland

In 10 patients with GH deficiency and signs of mild hypothyroidism (7x idiopathic, 3x craniopharyngeoma), we found increased basal plasma TSH levels. Diagnosis of GH deficiency was based on absent GH response to insulin and/or arginine without and with T_4 therapy, on high HGH induced N-retention and on good growth response to HGH therapy. Primary hypothyroidism had been excluded by T_4 rise after TRH and/or TSH stimulation and by poor growth response to T_4 therapy. TRH (200 $\mu\text{g}/\text{m}^2$ i.v.) led to an exaggerated TSH response in the 5 patients tested. This is in contrast to the results in 50 other GH deficient children with (a) normal TSH curves (isolated GH deficiency, n=23), (b) absent TSH response (pituitary hypothyroidism n=8), (c) delayed TSH rise (hypothalamic hypothyroidism, n=19). T_4 led to a normalisation of TSH in all but 2 patients with craniopharyngeoma. In these 2, diabetes insipidus was treated with pituitary extracts possibly containing substances crossreacting in our assay system. In the remaining 8 patients, elevated TSH levels were alternating with normal values suggesting a feedback mechanism between thyroid and pituitary gland. We assume that in some patients with hypothalamic disorders, TSH is secreted in a biologically less active form (subunits?) immunologically crossreacting with normal TSH. TRH may be necessary not only for the release but also for the formation of the normal TSH molecule.

14 PRODUCTION, METABOLISM OF FSH AND LH IN PUBERTY DISORDERS. N. MacLaren, F.A. Akesson, and S. Raiti. University of Maryland, Baltimore, U.S.A.

The production rates (PR) (IU/24 hours), metabolic clearance (MCR) (mls/min.) disappearance (T 1/2) (hours) and excretion rates (% excretion) and Plasma testosterone (T) and Δ^4 androstenedione concentrations (ng/100 ml) were measured in males with Precocious Puberty (PP), Delayed Puberty (DP), Hypopituitarism (HP) and Congenital Adrenal Hyperplasia (CAH).

LH	PR	MCR	T 1/2	%Excretion	T	Δ^4
Men	250-470	17-24	1.5	12-18	575+150	109 + 20
P.P.	459.2	28.3	1.5	1.2	445.8	38.2
D.P.	250	12.4	1.5	4.0	64.0	22.9
H.P.	84.6	5.5	-	14.7	41.6	90.6
CAH	114.5	3.6	1.5	3.1	98	378

FSH Men	18-50	8-12	6.0	20-30
P.P.	21.8	6.4	-	14.7
D.P.	18.3	5.5	5.5	13.7
H.P.	9.2	5.1	6.5	20.1
CAH	41.7	3.6	-	14.9

We suggest that (1) in initiating puberty the LH PR rise precedes the plasma T rise and (2) precocious puberty might be a disorder of LH production.

15 ESTIMATION OF PLASMA MELATONIN (MT) CONCENTRATIONS IN CHILDREN AND ADULTS DURING THE LIGHT AND DARK PHASES OF THE DAY.

Josephine Arendt, Luc Paunier and Pierre C. Sizonenko, Clin. Univ. de Pédiatrie, Genève, Switzerland.

MT extracted from 5 ml of plasma was bioassayed using its skin lightening effect on *Xenopus laevis* larvae. Less than 200 pg MT/ml of assay medium may be measured. 72.1 \pm 1 % (mean \pm SD) of added ^3H -MT and 72.3 \pm 9.5 % (mean \pm SD) of unlabelled MT are recovered by extraction. Antibodies to MT have been raised in rabbits by conjugating N-acetyl-5-methoxy-tryptophan to bovine serum albumin (BSA) and also thyroglobulin. Only the BSA antibody showed significant cross-reactions (N-acetyl-serotonin, 3.2 %, 6-hydroxy-MT, 4.6 %). The sensitivity range is similar to the bioassay. Dilution curves of plasma MT were parallel to the standard curve. Results were as follows (pg/ml): 1) Bioassay: Obese children, 10-15 yrs, both sexes, 12 h = 119 \pm 41, 24 h (artificial light) = 187 \pm 43; adults, both sexes, 12 h = 177 \pm 94, 24 h (artificial light) = 189 \pm 51; male adults, 12 h = 147 \pm 50, 24 h (obscurity 20-24 h) = 861 \pm 514. 2) Radioimmunoassay: Male adults, 12 h = 445 \pm 96, 24 h (obscurity 20-24 h) = 742 \pm 156. Preliminary results seem to indicate that plasma MT levels found in obese children were not higher than those found in adults.

16 THE MECHANISM OF THE T3 RESPONSE TO PARTURITION. J. Sack, M. Beaudry, P. Delamater, W. Oh, & D. A. Fisher, Dept. of Pediatrics, UCLA-Harbor General Hospital,

Torrance, California, U.S.A.

We reported in the human newborn that the TSH and T3 increases in serum might be due to extrauterine cooling. To study this we have used the newborn sheep. Five groups were studied. Skin and rectal temps. were monitored, and FFA, T_4 , and T3 measured in serum.

Group I: (n = 8; mean gest. age: 143 d; mean birth wt. 3.1 kg) delivered into air, 20-22° C., cord cut immediately.

Group II: (n = 9; 143 d; 4.3 kg) delivered into 39° water (60 min) and then room air with cord intact (60 min).

Group III: (n = 4; 144 d; 3.7 kg) delivered into air; cord cutting delayed 60 min.

Group IV: (n = 4; 142 d; 4 kg) same as group II; TRH given at 60 min.

Group V: (n = 4; 142 d; 3.3 kg) same as group II; T3 given at 60 min.

Newborn lambs in room air showed a marked increase in T3 and FFA. T_4 increased more slowly. As long as the cord was intact T3 and FFA were unchanged in spite of cooling; after cord cutting T3 and FFA increased. Shivering did not prevent body cooling. TRH caused a delayed (4hr.) increase in T_4 and T3. T3 augmented the FFA response and produced a more rapid increase in body temp.

We conclude: 1) cord cutting is the primary stimulus increasing T3 and FFA in the newborn; 2) 60 min. FFA and T3 levels correlate with minimum rectal temp.; 3) T3 potentiates the FFA response; 4) the rapid increase in T3 does not seem to be due to TRH, and may be due to increased T_4 -T3 conversion.