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In vitro characterization of angiotensin mediated ACTH release

We recently demonstrated that angiotensin II(AII)directly mediates in vitro ACTH secretion in rat pituitary cells.To investigate the structure activity relationship of the AII molecule and intracellular events involved in AII mediated ACTH release we studied: 1)the ACTH stimulatory activity of the AII fragments AII(2-8),AII (3-8)and AII(4-8) 2)the effect of isobutyl-3-methylxanthine(IBMX)an adenyl cyclase inhibitor,prostaglandin E_2(PGE_2)and cyproheptadine on AII mediated ACTH release.Anterior rat pituitaries were enzymatically dispersed in trypsin/DNAase solution and placed in monolayer cell cultures.After 3 days of incubation,the cells were washed and incubated for 4 hrs in test media which was later assayed for ACTH by RIA.AII(10nM)elicited a 150-180% increase of ACTH secretion over control cells.A declining ACTH releasing activity was demonstrated with each consecutive C terminal aminoacid deletion from AII.AII with IBMX(1mM)released more ACTH over its control (IBMX alone)than the ACTH released by AII over its control($p<0.01$). PGE_2(1μM)decreased AII mediated ACTH release($p<0.01$).Cyproheptadine (1μg/ml)did not alter AII mediated ACTH secretion.In summary the relative potencies of AII C terminal deletion are AII>AII(2-8)>AII (3-8)>AII(4-8).IBMX potentiates,PGE_2 inhibits,and cyproheptadine has no effect on AII mediated ACTH release.Thus the C terminal aminoacids of AII are important to its ACTH stimulatory activity.It is suggested that higher intracellular C'AMP sensitized AII mediated ACTH release and PGE_2 may be a factor in this process.

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Endocrinologic, biochemical and histologic characterization of an ectopic ACTH producing carcinoma in childhood.

We studied a 10 yr old boy with Cushing's syndrome due to an ACTH secreting islet cell carcinoma of the pancreas. He had rapid weight gain, abdominal distention, proximal weakness but no hirsutism or striae. Height was -1 SD, weight was +2 SD and BP 130/90. Serum cortisol was 50-95 μg/dl without diurnal variation. Urinary free cortisol was 840 μg/24 hrs and not suppressed by dexamethasone. Plasma ACTH was strikingly elevated and secreted episodically at 900-1600 pg/ml with similarly elevated βLPH. Plasma calcitonin, LDH and α-fetoprotein concentrations were elevated. Hypokalemic alkalosis was present with normal plasma aldosterone but elevated renin and DOC. Plasma insulin to glucose ratio was normal. CT scan showed areas of punctate calcification in tail of pancreas. A tumor in the tail of the pancreas with extensive tumor nodules over the serosa was found. Tumor and both hyperplastic adrenals were removed to ameliorate Cushing's syndrome. An islet cell carcinoma was diagnosed histologically. Immunohistochemistry localized ACTH and insulin throughout the tumor. Tumor contained large amounts of βLPH by RIA. SDS gel electrophoresis of immunoprecipitated cell free translation products coded by tumor mRNA indicated that ACTH and βLPH arose from a common precursor molecule of 35000 daltons. A second patient, a 10 yr old girl with the same type of ACTH secreting islet cell CA was studied in 1957.

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Transient hypergonadotropic hypogonadism, SHBG deficiency and hyperprolactinemia in children with ALL during induction chemotherapy.

The hypothalamo-pituitary-gonadal axis was investigated in 4 pubertal boys (P 4-5) and in 2 prepubertal girls with acute lymphocytic leukemia (ALL). LH, FSH, PRL, the response to LHRH/TRH as well as testosterone (T), estradiol (E_2) and sex-hormone-binding globulin (SHBG) were measured in each patient before therapy, on day 10 and 21 during, and 7 and 30 days after induction therapy. T, E_2 and SHBG decreased in all patients together with a reduction in testicular volumes in pubertal boys (from 20-25 ml to 12-15 ml).

	T (ng/100 ml)		(E_2 pg/ml)		(SHBG (nmol/l binding sides)	
	before	21d	before	21d	before	21d
boys	154±76	32±19	45±16	10±1	27±13	16±5
girls	20± 8	5±0.1	20± 7	11±1	70±11	32±5

Transient hypergonadotropic hypogonadism occured (mean LH from 9 mIU/ml to 18 mIU/ml, mean FSH from 7 mIU/ml to 15 mIU/ml) within 21 days of treatment. Simultaneously, mean prolactin levels increased from 8 ng/ml to 17 ng/ml together with an increased response to TRH stimulation. We conclude that during induction therapy in children with ALL a transient hypergonadotropic hypogonadism occured induced by a decreased steroid synthesis at the gonadal level and/or by a decreased SHBG synthesis.

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Transient precocious puberty in an 11 month old infant.

In sexual precocity hormone secretion and sexual maturation can be halted with drug therapy, but will resume after therapy withdrawal. We have encountered a girl who had developed puberty at age 6 months and experienced menarche at age 11 months. FSH and LH concentrations (LER 907) were elevated and showed an adult pulsatile secretion pattern. LHRH response was markedly exaggerated as compared to normal puberty. Daily injections of long-action LHRH analog for 10 weeks caused suppression of gonadotropin and estrogen secretion and reversal of pubertal signs. During subsequent 18 months off therapy no recurrence of puberty has been observed. FSH-LH pulsatile secretion did not recur, LHRH response was lessened, vaginal maturation indices did remain prepubertal, growth and skeletal maturation paralleled normal.

	basal			peak post LHRH		
Therapy	pre	during	post	pre	during	post
FSH uIU/ml	4.9	1.1	2.4	14.1		26.0
LH uIU/ml	2.8	0.3	0.3	16.0		4.7
E_2 pg/ml	37	<20	<20	42	<20	<20

It is proposed that the cause of transient precocity was due to hypersensitivity to LHRH. Therapy with LHRH analog while effectively suppressing puberty is not considered causative for the subsequent remission.

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Cognitive function and personality features in Turner syndrome.

Conflicting data about cognitive pattern and personality in cases of Turner S. are reported in literature. We have assessed 36 female (3-21 uears) with WISC, WAIS, Bender, H.T.P. and Corman's family tests. 18 of these subjects were affected by Turner syndrome (45XO; 45XO/46XX; 46Xi (Xq); 45XO/46 Xi (Xq); 45XO/46XXp-; 46XXq-); 18 controls were matched as to the age, place of origin, educational and social status.

The controls have been tested in their own environment by the same psycologist.

Results: 1) No correlation has been found between IQ and different chromosomal complement. 2) A significant deficit of Performance IQ has beeen confirmed while no significant differencies have been found as to Verbal IQ and visual-spacial performances in Turner S. vs. controls.

Conclusion: From our data it could be suggested that in Turner syndrome VIQ is more strictly correlated with personality and environmental factors than with the syndrome itself.

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Early diagnosis of Kallman's syndrom in male infants.

The Kallman's syndrom is usually evocated at adolescence in front of the association of delayed puberty and anosmia. We recently observed 3 infants with extreme micropenis and bilateral cryptorchidism, in whom the diagnosis of Kallman's syndrom was suspected on 1) low plasma testosterone level (<0.15 ng/ml) and fail of this one to increase either spontaneously during the first trimester of life or after hCG stimulation test (3 X 500 U) 2) low basal LH value (<1.4 mU/ml) with insuffisant rise (<3.9 mU/ml) after LHRH (0.1 mg/m^2) at 2 months of age. In addition a familial evocative history was present in the 3 cases. The mother of one infant was followed for a Kallman's syndrom. Anosmia with or without cryptorchidism was noted in the familial history of the 2 others. These data indicate that 1) because of evocative clinical and biological features the diagnosis of Kallman's syndrom may be made early in infancy 2) an autosomic dominant mode of inheritance of this syndrom is involved.