

3 EFFECT OF GROWTH HORMONE RELEASING FACTOR (GRF) ON PLASMA GROWTH HORMONE (GH) AND PROLACTIN (PRL) LEVELS IN OBESE CHILDREN.

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Obese children have a blunted GH response to conventional pharmacological stimuli. To assess whether this blunted response has a hypothalamic or pituitary origin, the response of plasma GH to a glucagon stimulation test (0.1 mg/kg IM) and to a single IV bolus of 0.5 µg/kg of GRF was studied in 13 obese children [145 ± 7% (SEM) of ideal body weight (IBW)] and compared to that of 19 lean (93 ± 4% of IBW) short children with normal pituitary function (N). Peak GH response to glucagon was lower in obese than in N children (16.0 ± 2.0 vs 29.2 ± 4.5 ng/ml, $p < 0.001$) as was the GH response to GRF (12.4 ± 2.6 vs 39.2 ± 5.1 ng/ml, $p < 0.001$); the GH response to GRF tended to be more prolonged in obese than in N children. In neither group was there a correlation between peak GH after GRF and percentage of IBW or age. There were no acute changes in PRL levels after GRF in neither group: a normal decrease was observed between 9 and 11 AM (from 201 ± 48 and 211 ± 49 µU/ml to 146 ± 31 and 108 ± 27 µU/ml in the obese and N group, respectively). Conclusion: obese children have a blunted and prolonged GH response to GRF; this blunting is not correlated with age and is not associated with an acute increase in PRL levels, as seen in children with hypothalamic hypopituitarism (Ped Res 18: 1216, 1984) and thus probably results from a different mechanism, perhaps at the pituitary level.

4 VARIATIONS OF PLASMA GRF LEVELS DURING GH STIMULATION TESTS IN CHILDREN.

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GRF was measured by RIA in the extracted plasma of 27 constitutionally short children given an oral dose of L-DOPA or aminoacid infusion (ornithine or arginine). After an overnight fast and one hour rest, basal GRF levels were 47 ± 7 (SEM) pg/ml. In 5 children L-DOPA induced at 15 min. a GRF increase from 47 ± 5 (SEM) pg/ml to 96 ± 15 (SEM) pg/ml followed by a GH increase at 60 min. from 2 ± 0.5 (SEM) ng/ml to 12 ± 2 (SEM) ng/ml. In 4 others no increase in either GH or GRF occurred after L-DOPA. In these 9 children the peaks of GH and GRF were strongly correlated ($r = 0.841$, $p < 0.001$). On the opposite, the aminoacid-induced GH release was not preceded by a GRF rise but was followed by a GRF decrease from 51 ± 10 (SEM) pg/ml to 27 ± 4 (SEM) pg/ml, $p < 0.02$. We conclude that GH stimulation tests may act in two different ways and that GH levels could be involved in the feedback control of GRF secretion.

5 THE EFFECT OF AGE ON SOMATOSTATIN (SRIF) SUPPRESSION OF GROWTH HORMONE (GH) RELEASE FROM RAT ANTERIOR PITUITARY CELLS IN VITRO. L. Cuttler, J. Welsh, M.

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Plasma GH levels are high in newborn rats and fall dramatically soon after birth. The etiology of this developmental pattern, which is similar in other mammals, is not known. We tested the effect of SRIF on basal, GRF-stimulated, and (Bu)2cAMP-stimulated GH release in monolayer cultures of anterior pituitary (AP) cells from 2d old (n=64), 15d old (n=11), and adult female (n=5) Sprague-Dawley rats. 0.33 nM SRIF (ED50) decreased GH secretion to 72 ± 8, 78 ± 4, and 42 ± 6% of control values in 2d, 15d, and adult AP cells, respectively ($P < 0.05$ for age effect). As stimulated secretion of GH is more sensitive than basal to the suppressive effect of SRIF, 0.33 nM SRIF was also tested in combination with 1nM GRF and 0.5mM (Bu)2cAMP. In 2d, 15d, and adult AP cells, GRF increased release 5.8, 4.4, and 3.6 fold over basal, while (Bu)2cAMP increased it 4.5, 2.7, and 3 fold. In these respective age groups, SRIF suppressed GRF-stimulated GH release to 79 ± 2, 57 ± 4, and 36 ± 2%, and (Bu)2cAMP-stimulated GH release to 88 ± 3, 63 ± 6, and 19 ± 1% of that with the stimulator alone. The effect of SRIF on both GRF- and (Bu)2cAMP-stimulated GH secretion varied significantly with age ($P < 0.001$). Conclusions: In rats, the ability of SRIF to inhibit both basal and stimulated GH release is strikingly age-dependent, SRIF exerting greater suppression in adult than in immature AP cells. Relative resistance to SRIF in young rats may contribute to high plasma GH levels during early development.

6 GROWTH HORMONE GENE DELETION WITHOUT GROWTH ARREST.

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Isolated growth hormone deficiency type 1A (IGHD 1A) is caused by deletion of the hGH-N gene. As described in Swiss pedigrees, antibody development and growth arrest complicate hGH treatment. We used restriction endonuclease analysis to detect hGH-N deletion among Oriental Jewish children with IGHD and then examined responses to hGH treatment. Patients in 4 families were products of consanguineous matings. They were homozygous for deletion of the hGH-N gene as shown by absence of characteristic, hybridizing, Bam HI and Hinc II fragments. Abnormal size Hind III fragments indicated deletions of 7.5 kb. Polymorphic Bgl II and Msp I patterns differed in patient 4, suggesting that at least 2 different events had produced deletions of similar size. Growth data are shown below:

Pre Rx	Pt.	Sex	Age	Ht. cm	-SDS	Post Age	Ht. cm	-SDS	hGH ab's
1	M	4.5	74.6	6.6	Rx	17	161.0	2.1	No
2	M	2.5	66.0	6.0		16	154.3	2.4	No
3	F	0.9	60.2	4.4		8.2	114.5	2.1	?
4	F	1.1	59.6	6.4		2.8	78.0	3.4	?

Despite extreme pre-Rx height deficits, growth responses to hGH treatment were good. Antibodies did not appear or did not impede growth. We conclude that factors other than gene deletion contribute to formation of blocking antibodies to hGH. Growth failure during treatment is not a sensitive marker for IGHD 1A. Diagnosis requires study of patients' GH genes.

7 ORAL TREATMENT OF CENTRAL DIABETES INSIPIDUS (DI) IN CHILDREN BY DDAVP TABLETS. A. Fjellestad, R. Rappaport, P. Czernichow. Unité d'Endocrinologie Pédiatrique et Diabète. Hôpital des Enfants-Malades, Paris.

Although nasal administration of DDAVP is very efficient there are several situations where this route is not feasible. This work was undertaken to test the feasibility of oral DDAVP administration, in 10 children (3 to 17.5 yr) with DI of various etiologies previously treated with intranasal DDAVP. In the first part of this study patients were hospitalized and increasing doses of oral DDAVP tablets (12.5 to 800 µg) were given every 12 hrs. Urinary volume and osmolality (U Osm) were measured in order to establish a dose response curve. In a 2d part oral treatment was continued at home for 3 months with the efficient dose as determined initially.

Antidiuresis started 45 min after oral DDAVP and reached a maximum after 120 min. A log linear relationship was demonstrated between DDAVP dosage and duration of antidiuresis. A 9 to 11.5 hrs antidiuresis (U Osm 550 to 650 mOsm) was obtained with larger doses. During the 2d period some children were treated with that amount administered twice a day but 7 of them were better treated with lower doses given 3 times a day. All patients and their parents preferred the oral route.

In conclusion, oral administration of DDAVP is possible and offers an alternative to the intranasal administration when this route is not efficient (rhinitis essentially). This study demonstrates that a nonapeptide can be absorbed by the intestinal tract and retain its biological activity.

8 THYROTROPIN RECEPTOR ANTIBODIES (TRAb) IN PATIENTS WITH JUVENILE GRAVES DISEASE (JGD) Thomas P. Foley, Jr., Carlie White and Antonia New University of

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To determine if serum TRAb measurements are useful in diagnosis and management of JGD, we studied 48 pts with JGD & 113 controls: 41 adults; 41 children & 31 with Hashimoto's Disease (HD), 9 with ↑ TSH levels. We tested 3 groups of JGD pts, I: active and untreated disease; II: recurrent disease; III: in remission on no therapy. TRAb was measured by displacement of labeled bTSH from porcine thyroid membranes (Cl. Endocr. 20:539, 1984), and values expressed as % inhibition of tracer TSH binding. RESULTS:

TRAb	Adults	Children	HD	HD ↑ TSH	JGD-I	JGD-II	JGD-III
n	41	41	31	9	27	16	36
X	+1.8%	-1.1%	-0.3%	-0.5%	+48%	+30%	+6%
Range:	-9 to +10%	-12 to +7%	-10 to +9%	-13 to +11%	+4 to +97%	+5 to +102%	-14 to +67%

No antidiagnostic antibodies were detected. There was no correlation between TRAb and TSH in HD with ↑ elevated TSH. False negative TRAb results occurred in 2 JGD-I (7%) pts and 1 JGD-II (6%) pt; false positive TRAb results occurred in 6 JGD-III (17%) pts, and were not associated with relapse of the disease.

In conclusion: Abnormal TRAb values will confirm the diagnosis of JGD in > 90% of pts with hyperthyroidism, and are found in > 90% of JGD pts in relapse. TRAb values are greater at initial diagnosis than during relapse, probably reflecting a shorter duration and less severity of disease during relapse. Abnormal TRAb values during remission may result from TRAb without thyroid stimulation, or the development of co-existing HD.