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SUPPRESSION OF LH SECRETION IN PRECOCIOUS PUBERTY WITH DEPOT FORMULA AND DAILY INJECTIONS OF GNRH ANALOGUE LEUPROLIDE ACETATE (PROCRENE)

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There has been some concern about the suppressive effect of daily inj. of GnRH analogues on LH secretion in the treatment of CPP.To evaluate the difference between Procrene 1 mg daily as bedtime inj.and monthly 3,75 mg depot inj.,12 h overnight LH secretion profiles were made in 9 children with CPP,3 treated with daily inj.and 6 with depot inj. 30 min.samples contin.suction.All patients treated at least 3 months. The tables give the results.Limit for prepubertal LH $\leq$ 3.0 IU/l.

PAT.NO	1	2	3	4	5	6	7	8	9
THERAPY	DAILY 1 mg			MONTHLY DEPOT 3.75 MG					
TESTNO 1	7.0	3.3	2.3	<0.3	<0.3	<0.3	0.5	0.8	0.6
2	6.8	3.1	2.3	<0.3	<0.3	<0.3	<0.3	0.9	<0.3
3	6.7	3.1	2.3	<0.3	<0.3	<0.3	0.5	0.8	<0.3
4	6.6	2.7	2.3	<0.3	<0.3	<0.3	<0.3	0.8	<0.3
5	6.4	2.6	2.3	<0.3	<0.3	<0.3	<0.3	0.8	<0.3
6	6.1	2.7	2.0	<0.3	0.3	<0.3	0.8	0.8	<0.3
7	6.0	2.7	1.8	<0.3	0.5	<0.3	0.5	0.7	<0.3
8	5.5	2.5	1.9	<0.3	0.5	<0.3	<0.3	0.7	<0.3
9	5.3	2.5	2.1	<0.3	0.5	<0.3	0.6	0.7	0.5
10	4.8	2.4	1.8	0.3	<0.3	0.3	0.6	0.8	<0.3
11	4.6	2.3	1.8	0.3	0.6	0.6	0.5	0.8	<0.3
12	4.4	2.2	1.9	<0.3	0.5	0.7	0.5	0.7	<0.3
13	3.7	2.3	1.7	0.3	0.5	0.8	0.5	0.8	<0.3
14	3.0	2.2	1.6	<0.3	<0.3	0.7	0.7	0.9	<0.3
15	3.7	2.2	1.5	<0.3	<0.3	0.6	0.8	0.8	<0.3
16	3.6	2.1	1.4	0.3	<0.3	0.9	0.7	0.9	<0.3
17	3.4	2.3	1.3	0.5	<0.3	0.7	0.7	0.8	<0.3
18	3.4	2.2	1.4	<0.3	<0.3	0.7	0.7	0.9	<0.3
19	3.1	1.9	1.3	0.3	<0.3	0.6	0.5	0.7	<0.3
20	3.1	2.0	1.3	0.5	<0.3	0.7	<0.3	0.7	<0.3
21	2.8	1.8	1.1	0.6	<0.3	0.8	<0.3	0.8	<0.3
22	2.6	1.7	-	<0.3	<0.3	0.9	<0.3	0.7	<0.3
23	2.2	1.7	-	<0.3	<0.3	0.8	0.5	0.8	<0.3
24	-	-	-	0.5	<0.3	0.9	-	0.7	<0.3

Conclusion:Depot formulas of GnRH analogues seem to be a more secure treatment for central precocious puberty than daily injections.

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INHIBITION OF GnRH SECRETION BY IGF-I DEGRADATION INTO A SUB-PRODUCT ANTAGONIST AT NMDA RECEPTORS : AN EFFECT DEVELOPING AFTER ONSET OF PUBERTY. J.P. Bourguignon, A. Gérard, M.L. Alvarez Gonzalez and P. Franchimont, Dept of Pediatrics and Radioimmunoassay Laboratory, University of Liège, Belgium.

We showed recently (JCI, 1992, in press) that, in hypothalamic explants of prepubertal male rats (15-day-old), NMDA receptors mediated a potent inhibitory control of GnRH secretion which was no longer observable at the onset (25 days) and by the end (50 days) of puberty. Sara et al (BBRC,1989,151:207) suggested that GPE, the N-terminal tripeptide of IGF-I, could play a role as competitive antagonist at NMDA receptors. Using explants obtained at 15, 25 and 50 days, we studied GnRH secretion induced by 5.10^{-4} M of veratridine, a depolarizing agent. This study was repeated in the absence or in the presence of increasing concentrations of IGF-I, GPE or des(1-3)IGF-I, a bioactive form of IGF-I resulting from clivage of GPE. At none of 3 studied ages, des(1-3)IGF-I showed any effect on GnRH secretion. At 25 and 50 days, IGF-I resulted in a dose-related inhibition of GnRH secretion (50 % inhibitory concentrations, IC_{50} : 8.10^{-10} and 2.10^{-13} M, respectively). A similar inhibition was observed using GPE (IC_{50} : 4.10^{-9} and 3.10^{-13} M). At 15 days, IGF-I did not result in any effect on GnRH secretion whereas GPE showed potent inhibitory action (IC_{50} : 1.10^{-13} M). At the 3 studied ages, GPE effects paralleled those of AP-5, a competitive antagonist at NMDA receptors. These data indicate that the hypothalamus is capable of degrading IGF-I into a subproduct which is a potent endogenous antagonist at NMDA receptors involved in GnRH secretion. This effect results from a developmental process in the hypothalamus since it is not observed in the immature rat. At onset of puberty, the endogenous IGF-I-derived antagonist at NMDA receptors could be involved in the disappearance of the inhibitory control of GnRH secretion. Supported by grants from FRSM (3.4574.87), Faculty of Medicine ULg and Kabi Pharmacia.

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CHARACTERIZATION OF THE MOLECULAR DEFECT IN THE VASOPRESSIN-NEUROPHYSIN II GENE IN A FAMILY WITH AUTOSOMAL DOMINANT NEUROHYPOPHYSEAL DIABETES INSIPIDUS D.R. Repaske and J.E. Browning, Division of Endocrinology, Children's Hospital Medical Center, Cincinnati, Ohio 45229-2899

Autosomal dominant neurohypophyseal diabetes insipidus (ADNDI) is a rare familial form of vasopressin-deficient DI. In previous studies, we have shown genetic linkage between ADNDI and the arginine vasopressin-neurophysin II (AVP-NP II) gene locus. This gene contains 3 exons that encode AVP, its carrier protein NP II, and a small glycoprotein. We obtained genomic DNA from a 25 yr old woman with longstanding DI, her 2 year old affected daughter, and her husband and unaffected daughter. Each of the three exons of the AVP-NP II genes of these individuals was amplified by polymerase chain reaction and sequenced by thermocycle sequencing. In the affected individuals, a single nucleotide mutation (C --> T) was detected in exon II of the AVP-NP II gene. The nucleotide sequence of exons I and III were completely normal. These affected individuals also have one normal allele of the AVP-NP II gene. The mutation encodes a Pro --> Leu substitution in the NP II protein. This mutation also destroys an Apa I restriction enzyme recognition site and creates a Dde I site. To ensure that this mutation is not a common, genetically silent polymorphism in the sequence of the AVP-NP II gene, we amplified exon II of 50 control individuals representing 100 AVP-NP II genes to screen for the presence of this nucleotide change. Neither absence of the Apa I restriction site nor presence of the Dde I site was detected in control individuals, suggesting that this mutation is the cause of ADNDI in the affected family. The mechanism by which vasopressin deficiency results from a mutation in one of a person's two NP II-encoding sequences is under investigation.

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ENDOCRINE OUTCOME OF SURGICAL REMOVAL OF CRANIO-PHARYNGIOMAS. J. Curtis, R.M. Ehrlich, D. Daneman, H. Hoffman, Dept. Pediatrics & Neurosurgery, U of Toronto and The Hospital For Sick Children, Toronto, Canada M5G 1X8

We reviewed the endocrine and surgical outcome of 34 cases (23 boys,17 girls mean age 8.8 yrs) of craniopharyngioma (C) initially operated on from 1980-89. One died,11/31 who had attempted total removal had a recurrence,12 have required no further procedures. 7 were followed elsewhere.Of 3 partial removals, 2 recurred. Vision improved in 48% new visual loss 18%, new field defects 24%.Adrenal insufficiency 89%. Hypothyroidism 96% and hypogonadism 100%. Diabetes insipidus occurred in 32, permanent in 31 Postop hyperglycemia 7, 2 required insulin temporarily Mean preop height Z score was -1.1(-3.8 to-0.39) 24% were below the 3rd % Mean preop weight Z score was 0.21(-2.9 to+8.4)16 cases became obese (increase in weight of >1 Z score) 4/17 with and 8/17 without increase in weight Z score required growth hormone(GH).On GH height Z scores improved -1.8 $\pm$ 0.38 to -0.8 $\pm$ 0.33($p<0.06$ NS). Conclusions Following attempted total removal of C almost all were hypopit,half became obese and 1/3 recurred. Most obese patients did not require GH

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L-THYROXINE INDUCED TSH SUPPRESSION. G. Radetti, G Tonini, S. Bernasconi, C. Volta, F. Rigon, Department of Pediatrics of Bolzano, Trieste, Parma and Padova, Italy.

Thyroid hormones (TH) suppress TSH release not only as a direct effect on the pituitary, but also by inhibiting hypothalamic TRH. Endogeneous somatostatin, dopamin and calcium seem also to play a role. 25 adolescents (5 M, 20 F) receiving high doses of l-thyroxine (3 µg/Kg/day) for endemic goiter were subdivided in 3 groups (A,B,C) and studied in two phases: in the first phase a TRH test (200 µg i.v.) was performed and TSH, PRL and GH samples taken at time 0', 20', 40' and 60'. In second phase (a week later) a similar TRH test was repeated, but group A (9 pts) was given 60 mg pyridostigmine bromide (a cholinergic agonist) p.os 60' before, group B (7 pts) received 10 mg metoclopramide (a dopamine antagonist) p.os also 60' before, and group C (9 pts) 40 mg of verapamil (a calcium antagonist) thrice daily for one week. Basal TH were: T3 1.8±0.7 ng/ml (nv 0.8-2), T4 12.3±3.1 µ/dl (nv 4.5-12), fT3 4.8±2.3 pg/ml (nv 2.5-6), fT4 2.5±1.0 ng/dl (nv 0.8-1.9). Results (basal and peak of 1st TRH versus 2nd TRH): in group A TSH was 0.3±0.3/0.5±0.5 µU/ml vs 0.2±0.2/0.6±0.4 µU/ml (NS), PRL was 8.9±8/22.4±11.6 ng/ml vs 6.8±6.1/23.3±12.4 ng/ml (NS), while a significant rise of GH 0.5±0.6/2.5±3.3 ng/ml vs 3.3±4.7/11.7±9.2 ng/ml ($p< 0.025$ for the difference between the peaks) was obtained during the 2nd phase and thus confirming the inhibition of somatostatinergic tone. In group B TSH was <0.1/0.2±0.3 vs <0.1/0.2±0.2 µU/ml (NS), a significantly higher rise of PRL was observed during the 2nd phase 10.4±3.3/21.6±12.6 ng/ml vs 9.4±3.9/58.4±17.1 ng/ml ($p<0.001$ for the difference between the peaks) due to a lowered dopaminergic tone, while no response of GH was seen 2.9±4.5/4.6±6.4 ng/ml vs 2.5±3.3/2.4±2.2 ng/ml (NS). In group C TSH was 0.1/0.2±0.3 vs 0.1/0.3±0.5 µU/ml, PRL 9.6±6/39.4±22.6 ng/ml vs 11.1±4.6/50±33.3 ng/ml and GH 3.5±1.9/4.1±2.4 ng/ml vs 4.4±3.1/4.1±2.3 ng/ml (NS for all). Conclusion: our results would confirm the hypothesis that the direct effect of the thyroid hormones on the TSH secretion seems to be more important than that mediated by somatostatin, dopamin and/or calcium.

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SIMILAR SECRETORY PATTERN IN GROUPS OF PATIENTS WITH THE SAME AMOUNT OF SECRETED GROWTH HORMONE.

In previous studies with normal subjects we have demonstrated a straight relationship between pulsatility and growth hormone (GH) secretion (1). To assess whether this relation is not specific to normal subjects, we have studied comparatively groups of patients in different pathophysiological states, but with the same degree of secreted GH. The patients studied were boys, classified in groups with high or low spontaneous GH secretion (GH-24h profile). Group I-high-secretion Ia: 14 prepubertal with low weight for height vs Ib; 21 normal pubertal. Groups II-low-secretion IIa: 11 obese prepubertal vs IIb: 11 prepubertal with GH deficiency and normal weight.

Spontaneous GH secretion was evaluated by 20 minutes sampling (Cormed pump). Pooled specimens were formed to measure 24h integrated concentration (IC-GH). The pulses (number and areas) and the area under curve (AUC) in the 24 h profile were estimated with the Pulsar program. Moreover, the pulses were classified as small or large depending on whether their amplitude was$\geq$ 4ng/ml. GH levels were evaluated by IRMA (Hybritech).

RESULTS:

	GROUP I		GROUP II	
	Ia	Ib	IIa	IIb
GH secretion				
IC-24h	3.21±1.1	3.0±1.1	0.7±0.2	0.7±0.3
AUC	164.6±44.2	173.8±71.0	50.8±19.2	42.6±20.4
max.pulse	19.4±8.2	18.6±9.6	6.50±4.5	7.19±2.5
N°of pulses				
Total	8.2±2.1	8.8±1.5	7.5±2.1	6.8±3.3
Small	3.0±1.1	3.0±1.9	5.2±3.0	5.1±2.8
Large	5.2±1.8	5.8±1.9	3.0±1.1	1.8±1.8

No statistical differences were found between mean values of subgroups, a and b in boin groups.

CONCLUSION:

Patients with the same amount of secreted GH show very similar secretory pattern despite their pathophysiological situation.

REFERENCE:

(1) Herrera et al. Horm.Res.(1992) 37 suppl.4,47.