493 EFFECTS OF HUMAN PANCREATIC GROWTH HORMONE RELEASING HORMONE (HPGRH) ON GROWTH HORMONE (GH) SECRETION IN PREGNANT AND FETAL RATS.

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Pregnant Holtzman rats were studied at 19 and 20 days gestation. Animals were anesthetized at -30 min with pentobarbitol 60 mg/kg IP. 5 ug HPGRH 1-44 or normal saline was administered IV at 0 min. Blood for maternal GH measurement was obtained via cardiac puncture at 0 min and following decapitation at 11 min. Fetuses were removed by C-section between 7 and 11 min and cardiac blood from littermates pooled for a single fetal GH determination. *$\bar{X}$±SD **ng/ml

Gestational Age	Treatment	Maternal GH**	Fetal GH**
19 days (N=4)	Saline	546±246* → 362± 106	18± 4
(N=5)	HpGRH	619±278 → 2606± 548	28± 12
20 days (N=6)	Saline	761±556 → 556± 396	237±123
(N=6)	HpGRH	591±627 → 1797± 413	141± 55

Mean maternal GH levels rose significantly ($p < 0.005$) in animals receiving HPGRH and were unchanged in those receiving saline. Mean fetal GH levels were significantly greater ($p < 0.005$) at 20 vs 19 days gestation. There were no significant differences between mean fetal GH concentrations of mothers receiving HPGRH and those receiving saline. HPGRH increases GH concentrations in the pregnant rat. HPGRH administration to the pregnant rat during late gestation does not increase GH concentrations in the fetus suggesting either that HPGRH does not cross the rat placenta or that the fetal rat pituitary is insensitive to HPGRH at this dosage.

494 EFFECT OF HYPERTHYROIDISM UPON HUMAN PANCREATIC GROWTH HORMONE RELEASING HORMONE (HPGRH)-INDUCED SECRETION OF GROWTH HORMONE (GH) IN THE ADULT MALE RAT.

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Four groups (n=8) of 300 g male rats received daily s.c. injections of saline, thyroxine (T4) 20 ug, T4 40 ug, or T4 80 ug for 14 days. 24 hrs following the last injection rats were anesthetized with pentobarbital (IP 50 mg/kg) at -30 min. 10 ug HPGRH 1-44 was administered I.V. at 0 min. Blood for GH determination was obtained via cardiac puncture at 0, 5 and 10 min. Rats were decapitated at 15 min; trunk blood was collected for measurement of GH, T4RIA, and T3RIA.

Group	Treatment	T4(ug/dl)	T3RIA(ng/dl)	GH(ng/ml) *$\bar{X}$±SD Basal	Peak
A	Saline	4±1*	34± 8*	474±533*	5520±2501*
B	T4 20ug	12±2	84±16	188±106	5495±1668
C	T4 40ug	15±2	201±36	188±143	5211±1600
D	T4 80ug	20±4	420±76	224±98	4701±1168

Average daily food intake was significantly greater in groups C and D than in group A ($P<.05$). Final mean body wgt varied inversely with the T4 treatment dosage (Groups C,D <A;$p<.01$). T4RIA and T3RIA concentrations were significantly greater in rats treated with T4 then in control rats ($p<.001$). There were no statistical differences between mean basal or peak GH responses to HPGRH among any of the groups.

Hyperthyroidism of brief duration does not alter the GH secretory response to a pharmacologic dose of HPGRH in the adult male rat.

† 495 GROWTH HORMONE NEUROSECRETORY DYSFUNCTION (GHND) IN THE SPECTRUM OF ENDOCRINE ABNORMALITIES IN CHILDREN WITH EMPTY SELLA.

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We examined 5 children with radiologic evidence of empty sella (patients 1-3) or partially empty sella (pts 4-5). Reasons for referral were short stature (SS), precocious puberty (PP) and 1° hypoparathyroidism (HPT). Evaluation of the hypothalamic-pituitary axis including provocative tests of TSH,PRL,LH,FSH,GH and cortisol secretion was undertaken in 4 of 5 pts.

Pts	Bone age	Diagnosis	Pit. studies-peak (test)
1(13.2yM)	15y	HPT	No abnormalities
2(16.9yF)	11-12y	SS	GH-2.1 ng/ml (L-DOPA,ITT, clonidine),PRL-2.0 ng/ml (TRH), LH-5.5 mIU/ml (LHRH)
3(11yF)	8-9y	SS	No abnormalities
4(13yM)	9y	SS	No abnormalities
5(7.8yF)	10-11y	PP	Not yet assessed

Classic GH deficiency was observed in pt 2. Normal provocative tests were observed in pts 3 and 4. Because of poor growth velocities, delayed bone ages and normal provocative tests, 24hr GH output was measured in the latter two pts. Mean 24hr GH level in pt 3 was 1.0 ± 0.0 ng/ml ($\bar{X}$±SE) with no significant (≥5 ng/ml) GH pulses observed. Mean 24hr GH level in pt 4 was 2.0 ± 0.4 ng/ml with only one significant pulse (peak=21 ng/ml) occuring at night. These results are low and consistent with GHND. Empty sella in childhood is associated with a spectrum of hypothalamic-pituitary abnormalities now including GHND.

● 496 PULSATILE GROWTH HORMONE (GH) SECRETION DURING PUBERTAL DEVELOPMENT IN INTACT AND CASTRATE MONKEYS.

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To assess whether pulsatile GH secretion changes during pubertal development, 23 intact and 21 castrate male macaques (rhesus and cynomologous) from prepubertal through adult life were evaluated. Blood was withdrawn at 15 min intervals for 12 or 24 hr through a femoral venous catheter. All animals were fit with a mobile vest and tether assembly. Pubertal development was assessed on the basis of chronological age, gonadotropin and testosterone secretion, testicular volume, hCG challenge tests and skeletal age. The pulsatile secretory GH data are summarized below:

Developmental age	$\bar{x}$ GH conc (ng/ml)	$\bar{x}$ peak GH conc (ng/ml)	No. GH pulses ≥5 ng/ml/12 hr
Intact			
Prepubertal (n=3)	8.5±3.0	17±3	5±0
Pubertal (n=6)	8.0±1.7	18±2	4±1
Adult (n=14)	7.7±1.0	20±2	4±0
Castrate			
Prepubertal (n=3)	7.0±4.7	14±6	4±2
Pubertal (n=3)	7.3±3.5	15±5	4±1
Adult (n=15)	5.7±0.9	17±3	4±1

These data suggest that pulsatile GH secretion does not change significantly during pubertal development in male monkeys and that endogenous testosterone does not alter pulsatile GH secretion.

● 497 FETAL CIRCADIAN RHYTHMS: CYCLES OF VASOPRESSIN (VP) LEVELS IN CEREBROSPINAL FLUID (CSF) NOT BLOOD.

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Besides classical effects on water balance and blood pressure, vasopressin has important functions in brain including modulation of behavioral processes and memory consolidation. In adult animals immunoactive VP in CSF exhibits a circadian pattern of release suggesting that the CSF may be a conduit for the effects of VP on diverse brain areas. To characterize the release of VP by the fetus, CSF was withdrawn continuously (1.0 ml/hr X 3 days) from the prechaismatic fossa of 5 chronically instrumented fetal sheep at 108 to 146 d gestation in 7 studies and plasma sampled intermittently (1.5 ml q 4h X 1 day) in 3 studies. Using a specific VP RIA, daily rhythms of VP in CSF were found for each fetus. Temporal profiles showed low levels of VP (12-25 pg/ml) during daylight alternating with high levels at night (30-45 pg/ml). Cycle length by frequency domain analysis was 22 to 24 hrs. No similar fluctuations in plasma VP levels (2.1±1.0 pg/ml) were found. The amplitude of the CSF rhythms was increased (125 pg/ml) with chronic hypoxia, acute hemorrhage and in the days immediately preceding term delivery.

We conclude that circadian rhythms of VP concentration in CSF but not plasma are present in the fetus during the final 25% of gestation. Changes in the amplitude and/or period of these rhythms may be important in the timing of parturition and the fetal response to suboptimal intrauterine condition.

● 498 TREATMENT OF TRUE PRECOCIOUS PUBERTY (TPP) WITH AN INTRANASAL (IN) LUTEINIZING HORMONE RELEASING FACTOR (LRF) AGONIST (A).

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Potent LRF Agonists administered subcutaneously (SC) or IN have proven useful in the treatment of TPP. We studied a new LRF-A, D Nal^6 LRF (Nafarelin acetate (NA), Syntex) in 7 girls (age 2-7y) and 2 boys (age 8-9y) with TPP (treatment duration 1.5-6 months (M)). NA 2µg/kg was given SC OD for 2 weeks (W) and 400µg IN OD thereafter. Plasma NA was measured by RIA after the first SC and IN doses. Plasma delta LH (ΔLH) and FSH (ΔFSH) after LRF 100µg IV, estradiol (E_2) and testosterone (T) were measured at baseline, 6W and 3M intervals thereafter. Results are summarized below as mean ± SEM (paired t test): at 6W, ΔLH 2.3±0.6ng/ml ($p<0.02$), ΔFSH 0.7±0.2ng/ml ($p<0.01$), E_2 23±7pg/ml ($p<0.04$), T 36ng/dl (n=2); at 3M, ΔLH 1.4±0.2ng/ml ($p=0.05$), ΔFSH 0.3±0.2 ng/ml ($p=0.025$), E_2 10pg/ml (n=2), T 7ng/dl (n=2) compared to baseline ΔLH 10.2±3.6ng/ml, ΔFSH 3.7±1.1ng/ml, E_2 53±12pg/ml and T 373ng/dl (n=2). Plasma NA levels peaked 20 min after SC NA (3.34±0.2ng/ml) and IN NA (1.88±0.7ng/ml) and were measurable (>0.05ng/ml) 8h after SC NA (9/9 patients) and IN NA (7/9). 6/7 girls had menses in the first M on treatment; however, no further vaginal bleeding has occurred. Growth velocity decreased from 11.7cm/y before treatment to 6cm/y after 6M (n=3).

Preliminary results suggest IN D Nal^6 LRF is an effective treatment for TPP in children.