140

CGD Brook, NA Bridges, DR Matthews, P C Hindmarsh.*
*Cobbold Laboratories, The Middlesex Hospital, LONDON, and * The Radcliffe Infirmary, OXFORD.*

SEXUALLY DIMORPHIC CHANGES IN LH SECRETION DURING CHILDHOOD AND PUBERTY.

We have examined changes in the pulsatile pattern of LH secretion that occur during childhood and puberty, using spectral analysis and a novel distribution method. 24 hour profiles of LH concentration were taken from 78 children aged 4.2-15.6yrs and 6 adult men. Relative Fourier transforms were derived, and a normalised estimate of the concentration below which each profile spent 5%(OC5), 50%(OC50) and 95%(OC95) of the total time of the profile was calculated. In children aged 4.2-9.8yrs, LH periodicity was 140-200 minutes. The OC5 in children aged 4.2-6.9yrs was greater ($p=0.05$) than in children aged 7.1-9.8yrs. In prepubertal children aged 10.1-14.8yrs, LH periodicity decreased to 100-120 mins ($p\leq0.025$), and OC50 and OC95 values increased ($p=0.01$, 0.003). LH periodicity in puberty was 120-160 minutes. In early puberty girls had greater OC5, OC50 and OC95 ($p=0.001$) and boys had greater OC95 ($p=0.04$), compared to prepubertal children. In late puberty OC values did not change for girls but OC5 and OC95 were greater for boys ($p=0.001$) compared with early puberty. OC values for both sexes in late puberty did not differ from the adult men.

CONCLUSIONS The decrease in LH secretion that occurs after the neonatal period continues as late as 4 years of age. Before the onset of puberty there was an increase in pulse frequency with an increase in peak but not baseline LH values. A mature pattern of LH secretion with elevated peak and baseline values was attained in early puberty in girls, but later in boys. This pattern may be important for fertility, and is the first time that sexual dimorphism has been described in the control of the onset of puberty.

141

HA Spoudeas, PC Hindmarsh, DR Matthews, CGD Brook
International Growth Research Centre, London UK

DISCREPANCIES BETWEEN PHYSIOLOGICAL AND PHARMACOLOGICAL TESTS OF GROWTH HORMONE (GH) SECRETION IN CHILDREN WITH BRAIN TUMOURS (BT)

We have performed a mixed longitudinal study of 59 spontaneous (24hr profiles) and stimulated (insulin-induced hypoglycaemia tests - ITT) measures of growth hormone (GH) secretion in 35 prepubertal children aged 1.5 to 11.2 years with BT distant from the hypothalamo-pituitary area before and at 6-12 monthly intervals up to 3 years after surgery ± radiotherapy ± chemotherapy. We have compared results with those obtained in 26 short normal controls (SN). The profiles were analysed by a distribution method. We observed discrepancies between peaks of spontaneous and stimulated GH in BT but not SN. The ratio was significantly greater in all BT groups compared to SN ($p<0.05$).

	pre	dxr	chem	surg	SN
N	16	26	10	7	26
Mean (sem)	2.62 (0.73)	2.61 (0.51)	3.03 (1.14)	3.47 (1.03)	0.99 (0.19)

Peak GH to ITT was not influenced either by the degree of hypoglycaemia ($r=0.1$, $p=0.65$) nor by days off dexamethasone therapy in those children assessed before radiotherapy ($r=0.24$, $p=0.37$). In 14 BT children in whom GHRH tests at 2 doses (1 μg/kg and 0.1 μg/kg) were performed, correlation with spontaneous peaks was greater with the low dose ($r=0.7$, $p=0.005$) than the high dose ($r=0.27$, $p=0.26$). A spontaneous/stimulated ratio approaching 1.0 suggests intact hypothalamic GHRH and somatostatin (SS) tone. ITT results reflect SS tone which was abnormal in children with BT. 24hr profile results reflect GHRH secretion and low dose GHRH tests identified this.

142

NA Bridges, PC Hindmarsh, DR Matthews, CGD Brook.*
*Department of Endocrinology, Middlesex Hospital, LONDON, * The Radcliffe Infirmary, OXFORD.*

THE EFFECT OF TWO DIFFERENT PULSE FREQUENCES OF GONADOTROPHIN RELEASING HORMONE TREATMENT (GnRH) IN THE INDUCTION OF PUBERTY.

It has been suggested that GnRH pulse frequency is important in the differential regulation of LH and FSH. We have studied the effect of two different pulse frequencies in the induction of puberty.

METHOD 5 girls and 3 boys were treated with GnRH by subcutaneous pulsatile pump, at frequencies of either every 45 minutes (fast) or 3 hourly (slow). 24 hour profiles of gonadotrophins and sex steroids were performed before treatment and after 5 days, 1, 3, 6 and 12 months. Treatment was continued for at least 12 months in all subjects, except one boy who dropped out after 4 months.

RESULTS The table shows mean 24 hour values for the groups at 5 days.

	LH(U/L)	FSH(U/L)	TEST(nmol/L)	E2(pmol/L)
PRETREATMENT:FAST	1.97	2.15	3.91	13.45
PRETREATMENT:SLOW	1.18	1.32	1.26	20.66
5 DAYS:FAST	2.81	3.05	3.99	32.37
5 DAYS:SLOW	1.71	1.96	1.44	39.88

There were no differences between the LH, FSH and sex steroid levels and in progress through puberty in the groups at any stage.

CONCLUSION While the pulsatile pattern of stimulation is important in the action of GnRH, pulse frequency does not appear to be important either in the differential regulation of LH and FSH or in progress in puberty.

143

HIGH DOSE ESTROGENS IN GIRLS WITH TALL STATURE INDUCE A TRANSIENT PROLACTIN INCREASE

ECAM Houdijk, HA Delemarre-van de Waal, Department of Pediatrics, Free University Hospital, Amsterdam, The Netherlands

Estrogens are a potent stimulus of prolactin secretion as illustrated by the increase during female puberty. High estrogen levels may lead to lactotroph hyperplasia and even pituitary adenoma. Prolactinoma in a girl treated with estrogens has been described (J Ped 1988,133:337-9).

Methods: In 30 girls with constitutional tall stature prolactin levels were measured before, during and, in part of them, after Ethinyl Estradiol (EE) therapy, 200 microgram/day. At the start of treatment mean age was 12.7 yrs (range 10.3-15.9) and pubertal stage was B3-B4: all were premenarcheal. Reference data were obtained from 25 healthy girls with mean age 13.4 yrs (range 11.7-15.1), pubertal stage B3-B5 and pre- or perimenarcheal. Blood was drawn between 9.00 and 12.00 am.

Results: In the control group mean prolactin was 0.19 U/l (range 0.09-0.37). In the EE group mean prolactin at the start of treatment was 0.19 U/l (range 0.05-0.51), not different from the control data. On EE (3-18 months) mean prolactin significantly increased (ANOVA $P<0.001$). Mean values at 3,6,9,12,15 and 18 months were 0.45, 0.41, 0.40, 0.33, 0.32 and 0.30 U/l respectively. The treatment values at each time were significantly higher compared to the control values as well (Wilcoxon $P<0.001$). After EE discontinuation prolactin values significantly decreased to 0.14 U/l (range 0.07-0.24), not different from pretreatment or control data.

Conclusion: High dose estrogen treatment results in prolactin hypersecretion, which normalizes after estrogen withdrawal. Follow-up of these girls should be done to exclude long-term consequences as hyperprolactinoma and/or prolactinoma.

● 144

SEXUAL DIMORPHISM OF GALANIN GENE EXPRESSION IN GROWTH HORMONE-RELEASING HORMONE NEURONS OF THE RAT DURING DEVELOPMENT. HA Delemarre-van de Waal, KA Burton, EB Kabigting, DK Clifton, RA Steiner. Depts of Ped, Free U. Hosp., Amsterdam, The Netherlands, and Ob/Gyn & Physiol/Biophys, U. Wash, Seattle WA 98195, USA.

Growth hormone (GH) secretion in the rat is sexually dimorphic, due, at least in part, to differences in the activity of growth hormone-releasing hormone (GHRH) neurons in the hypothalamus. Galanin (GAL), a small peptide that stimulates GH secretion in humans and rats, is coexpressed in GHRH neurons of the adult rat and this coexpression is sexually dimorphic. We investigated the changes in GAL coexpression in GHRH neurons over development in both sexes by performing double-label *in situ* hybridization on coronal sections from the brains of male and female 10, 25 and 70 day old rats. For GHRH and GAL mRNAs, we used cRNA probes labeled with digoxigenin and ^{35}S-UTP, respectively. GAL mRNA levels were measured by counting autoradiographic silver grains over individual GHRH mRNA-positive cells. The results, in grains/

Age	10-day	25-day	70-day
Male	6±1	15±7	54±4
Female	13±1	28±4	32±3

cell (±SE) are summarized above. GAL mRNA coexpression was significantly dimorphic at all ages. To test the hypothesis that this sexual dimorphism is related to plasma testosterone levels, we measured GAL mRNA levels in GHRH neurons of intact (I), castrated (C), and castrate plus testosterone (T)-replaced male rats. Castration reduced GAL message levels and T replacement prevented this reduction (73±6 (I), 58±4 (C), and 77±5 (C+T) grains/cell). **Conclusion:** GAL mRNA expression is sexually dimorphic in rats over development and this dimorphism is likely due, in part, to the presence of T in the male.

145

S.Willnow, W.Kiess, O.Butenandt, H.Dörr*, T.Negele, J.Egger, A.Enders, HP.Schwarz.
Dept. Pediatric Endocrinology, Children's Hospital, University of Munich, Munich, Germany,and *Childrens Hospital, University of Erlangen, Erlangen, Germany.

ENDOCRINE DISORDERS IN SEPTO-OPTIC-DYSPLASIA (DE MORSIER SYNDROME). The syndrome of septo-optic-dysplasia (SOD) is characterized by hypoplasia of the optic nerve, various types of forebrain defects and hormonal deficiencies. To better define the endocrine abnormalities in children with SOD we have studied the clinical and endocrinological characteristics of 16 such patients retrospectively. The children were seen in the pediatric endocrinology service at the Children's Hospital of the University of Munich from 1976 through 1992 (7 boys, 9 girls; age at initial presentation: 1 day to 13 years of age, mean 1.9 years). Mothers' age at delivery was between 16 and 32 years, mean 21.6. Seven of the 16 patients had neonatal hyperbilirubinaemia. Seven patients had perinatal problems with cyanosis and apnea which necessitated mechanical ventilation. Three neonates suffered from hypoglycaemia. Unilateral hypoplasia of the optic nerve was found in 5 cases, bilateral hypoplasia in 10. Sonographic, CT or NMR imaging yielded the following results: Five of the patients had a cavum septi pellucidi. Three patients had hypoplasia of the cerebellum, one aplasia of the corpus callosum and one aplasia of the fornix. An empty sella with or without an ectopic pituitary was seen in four cases. Height at time of diagnosis was -3.96 to +2.09 SDS, mean -2,38. Endocrine deficiencies were present in all 11 patients who had undergone endocrinological investigations. Seven patients suffered from GH deficiency (GH below 10 ng/ml in two provocative tests). One had diabetes insipidus centralis, one had hypogonadotropic hypogonadism, one had hypothyroidism and two adrenal insufficiency. Hypothalamic testing was performed in a subset of patients: in five of eight children tested a TRH test, in two out of eight a LHRH test, and in three out of five a GHRH test yielded abnormal results. High prolactin levels were measured in two out of five patients. In conclusion, (1) SOD is characterized by optic nerve hypoplasia and a variety of endocrine deficiencies. In addition, forebrain malformations are present in some SOD patients. (2) The putative hypothalamic origin of the hormonal disorders in some SOD patients needs to be investigated systematically. (3) Pediatric endocrinologists need to participate in the care of all patients with SOD.