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MELATONIN-INDUCED INHIBITION OF SEXUAL MATURATION IN THE MALE RAT: EVIDENCE FOR CENTRAL INHIBITION OF GnRH SECRETION.

We have shown that daily treatment with melatonin (MT) markedly delays sexual maturation in the male rat. The observations that MT-treated rats have normal pituitary responsiveness to GnRH and low or absent pulsatile release of LH pointed out for a central inhibitory action of MT on GnRH release. The sensitivity of MT-treated rats to gonadectomy and sex steroid replacement was investigated: male rats receiving 100 µg MT daily or saline were castrated at 30 d and immediately treated with various doses of testosterone propionate (T), or oil until sacrifice at 40 d. In animals that received oil, LH release was drastically reduced in MT-treated rats (46.0±7.3 ng/ml) as compared to controls (305±44) demonstrating that MT inhibits GnRH secretion in absence of sex steroid. Replacement with T showed that MT-treated rats were much more sensitive to T than controls, suggesting that MT potentiates the ⊖ feed-back action of T on LH release. Conversely, the ability of GnRH neurons of MT-treated rats to release GnRH in response to N-methyl-DL-aspartic acid (NMA), a excitatory amino acid analog known to cause LH release via GnRH, was found normal at 30 d since NMA (20 mg/kg BW, iv) elicited the same LH response in MT-treated and in control rats. These data further indicate that MT induces central inhibition of GnRH release without impairing secretory processes of GnRH neurons and prolongs the high sensitivity to sex steroid ⊖ feed-back typical of infantile animals.

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DIURNAL AND NOCTURNAL LH AND FSH SECRETION IN BOYS THROUGHOUT PUBERTY ESTABLISHED WITH A SENSITIVE IRMA.

LH and FSH values were studied in 30 healthy boys (CA:11.3-14.6 yrs, BA:10.3-16.2 yrs (TW2), Tanner stage G1-G5) Informed consent was obtained. Blood was sampled at 10' intervals from 12.00-18.00h and from 24.00-06.00h. An IRMA employing 2 monoclonal antibodies with a sensitivity of LH and FSH of 0.10 IU/l and 0.25 IU/l respectively was used. Testosterone (T) was measured every hour applying a RIA with a sensitivity of 1.0 nmol/l.Results of mean FSH, of mean LH, of mean LH pulse amplitude (pA), of LH pulse number (pN), of mean Nadir Interval in min.(NI) and of mean T are presented as the median per Tanner stage.

	DAY						NIGHT					
	FSH	LH	pA	PN	NI	T	FSH	LH	pA	pN	NI	T
G1	0.69	<0.1	-	-	-	<1	0.77	0.15	0.35	2	120	<1
G2	2.05	0.37	0.3	1	-	<1	2.01	1.77	1.55	4	70	<1
G3	2.69	0.86	0.8	1	-	<1	3.05	3.42	1.77	4	80	1.8
G4	2.76	0.87	0.5	2	130	1.4	3.28	3.93	1.68	5	65	10.5
G5	4.82	1.88	1.1	2	120	8.6	4.30	3.89	2.96	3	110	13.2

Conclusion: At the onset of puberty(G1) LH is undetectable during the day, while during the night LH is secreted in a pulsatile pattern. During puberty LH level, pA and pN increase, the night ahead. In G5 pN decreases, while pA still increases, presumable as a result of an increased negative feedback action of T. In contrast to LH, diurnal FSH is detectable in G1, shows a clear increase already in G2 and has no sleep-wake pattern.

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TIME LAGS BETWEEN VARIOUS MATURITY MEASURES AND SPERMARCHE.

On the basis of biannual examinations of 40 normal boys followed longitudinally for a period of up to 7 years (initially aged 8-11), the following maturity measures were studied: first occurrence of a testis size of more than 4 ml., pubic hair stage greater than Tanner stage one, broken voice, axillary hair greater than stage one, beard growth, occurrence of acne and the age of maximal height growth velocity and spermarche (onset of the release of spermatozoa).

Spermarche was estimated on the basis of occurrence of spermatozoa in quarterly collected 24-h urine samples, using the information of first occurrence of spermaturia and the frequency of intermittent occurrence of spermaturia after the first.

With confidence limits of about ± 4 months, the maturity measures showed the following time lags. Prior to spermarche: testis size >4 ml (16 months), pubic hair stage>1 (10½ months), first occurrence of broken voice (½ month). After spermarche: max. height growth velocity (5½ months), axillary hair stage>1 (8 months), growth of beard (12 months) and occurence of acne (13 months).

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The United Kingdom GnRH analogue Collaborative Study Group. (Introd. by C. G. D. Brook).

INTRANASAL (D-Ser^6) GnRH ANALOGUE FOR THE MANAGEMENT OF CENTRAL PRECOCIOUS PUBERTY.

We have treated 61 children (51F, 10M) with central precocious puberty using intranasal (D-Ser^6) GnRH analogue (Buserelin). Maximum duration of treatment was 3.7 yrs in the girls and 3.0 yrs in the boys. Mean dose (SD) of (D-Ser^6) GnRH was 25.3 (9) µg/kg in the girls and 18.6 (12) µg/kg in the boys.

No side effects were seen. 5 patients stopped treatment due to non-compliance. Of 27 children who had puberty stage 2 - 3 before treatment, 20 arrested or regressed and 7 advanced. Of 21 children treated at stage 4 - 5, 7 regressed and 14 had no alteration. Mean testicular volume in the boys was reduced from 9.2 (6) mls to 5 (1.4) mls after 1 year of treatment.

Mean basal serum LH became elevated during treatment, although there was a decrease in peak stimulated LH concentrations.

▲BA/▲CA fell during the first year of treatment to below 1.0. Height velocity in the girls reduced from 9.0 - 6.0 cms/yr during the second year of treatment. Height for bone age SDS increased from -1.86 (1.5) to -1.1 (1.5) during the first 1.5 yrs of treatment in the girls which was not significantly different from untreated controls.

Intranasal (D-Ser^6) GnRH is an effective treatment for central precocious puberty but does not alter height prognosis.

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PUBERTAL DEVELOPMENT AND FINAL HEIGHT IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY (CPP) AFTER THERAPY WITH THE Gn-RH ANALOG D-TRP-6-LH-RH.

Fifteen girls with CPP who have been treated with D-TRP-6-LH-RH (13 daily s.c.; 2 monthly i.m.) for 1 to 5 yrs were followed after therapy for 6 months to 4 yrs. Resumption of pubertal development was evident clinically 2 to 4 months after therapy was stopped and menstruation appeared after 3-6 months in 13 and after 2 yrs in one. In all growth velocity increased in parallel to pubertal reactivation and bone maturation advanced at a moderate rate. So far 8 girls have reached their final height.

	At Start of Therapy			
Pt.	C A	B A	Predicted Final Ht.	Achieved Final Ht.
	y:m		cm	cm
1	6:3	10:6	140.6	157.0
2	8:2	11:3	141.7	153.5
3	8:4	12:0	158.5	158.5
4	8:0	12:0	151.6	152.6
5	9:0	13:3	142.7	146.5
6	10:6	12:6	151.4	154.0
7	10:9	13:0	141.7	144.8
8	10:10	13:0	137.9	142.5

Our data indicate that Gn-RH analog therapy in CPP has a beneficial effect on final height when started at an early bone age. The genetic stature is also a determining factor in final height.

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TREATMENT OF PRECOCIOUS PUBERTY BY INTRANASAL D-SER (TBU)^6 LHRH1 - 9EA^{10}(BUSERELIN).

GnRH analogues afford effective, selective, reversible inhibition of pituitary gonadotropin secretion. We administered Buserelin (300 ug x 6/die) to 18 girls affected by precocious puberty, for 6-24 months (onset of first symptoms before 8 years of age). We evaluated Buserelin's effects on pituitary-gonadal, pituitary-thyroid, pituitary-adrenal function, ultrasonographic pelvic organs and thermographic mammary patterns, clinical and auxological features. Results: significant decreases (paired t test) were observed in: both LH and FSH reserves (LHRH test) and basal FSH since the first month (m) of treatment, E2 (3rd m), Progesterone (6th m); also TSH reserve (TRH test) since the 6th m, T3 (12th m) and fT3 (6th m) decreased significantly, though remaining in control range. T4, fT4, PRL, ACTH and adrenal hormones did not change significantly. Ultrasonography of the pelvis showed significant decreases of uterine (6th m) and ovarian (12th m) volume; the ovarian structure did not progress and follicle diameter was always 9 mm. Clinical/thermographic evaluation of the breast showed a generalized arrest or regression of its maturational patterns. Auxological data (slower bone maturation and growth velocity, lower SD scores for chronological and bone age, adult height prediction tending to improve) suggested a good prognosis. We conclude that these results of intranasal Buserelin administration and the absence of serious side effects make it advisable in the treatment of girls with true precocious puberty.