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Testicular responsiveness
to human chorionic gonadotrophin
in growth hormone deficient pre-pubertal boys:
lack of effect of replacement therapy

By

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The effect of hGH therapy on testicular response to hCG was studied in 7 pre-pubertal boys with known growth hormone deficiency. Each boy received 2000 IU hCG intramuscularly for 3 consecutive days either before starting hGH therapy or 4 months after temporarily discontinuing hGH therapy. A second 3 day series of hCG injections was administered after each boy had received 4 months of hGH treatment. Before each hCG challenge, serum concentrations of testosterone, LH and FSH were obtained and an iv GnRH test was performed. Growth hormone treatment either maintained or established linear growth velocities equal to or greater than expected for the patient's skeletal age. Testicular response off hGH therapy, either maximum serum concentration of testosterone or maximum rise above baseline, was not significantly different than testicular response while on hGH therapy. Testicular responses did not correlate significantly with either basal concentration of gonadotrophins or gonadotrophin responses to GnRH. Despite its effectiveness in stimulating growth, hGH did not effect testicular responsiveness to hCG in pre-pubertal boys with hGH deficiency.

Key words: growth hormone – testis – testosterone – Leydig cell.

The possibility that human growth hormone (hGH) might play a role in testicular function is suggested by observations of abnormal pubertal development in growth hormone deficient males and by recent investigations of GH effects on testicular function in other mammals. Zachman (1975) observed that testicular testosterone response to hCG improved after hGH therapy in adult male with isolated GH deficiency, and Laron & Sarel (1970) have reported that males with isolated growth hormone deficiency often have small external genitalia. Since foetal growth of male external genitalia is dependent on androgen production, small size of the external genitalia could reflect less than normal production of androgens during this development phase. In rats and hamsters, studies on testicular membrane preparations have demonstrated that the testicular LH receptor concentration is, in part, dependent on growth hormone. (Zipf et al. 1977; Bex & Bartke 1977; Odell & Swerdloff 1976; Zipf & Berntson 1981).

To investigate the possibility that hGH might influence human testicular function, we determined basal serum concentrations of gonadotrophins, gonadotrophin responses to synthetic gonadotrophin-releasing hormone (GnRH) and testicular responsiveness to hCG in 7 boys with growth hormone deficiency while on and off hGH therapy.

Materials and Methods

Seven boys with isolated hGH deficiency or multiple pituitary deficiencies were studied (Table 1). Three boys (Group I) had been receiving hGH for 2.5 years and were currently on hGH therapy (patients 1,2,3); the other 4 boys (Group II) had never received hGH treatment (patients 4,5,6,7). All patients with known deficiencies of TSH or ACTH were begun on appropriate replacement at least one month before the study. Human growth hormone therapy, 2 IU im 3 times per week, (Monday, Wednesday and Friday) was administered during the treatment period and this schedule was continued during the 'on therapy' study. Patients in each group were hospitalized in the Clinical Research Unit at the University of Michigan on 2 occasions separated by 4 months: once while on hGH therapy and once while off hGH therapy. The 'off hGH' study for Group I was performed 4 months after temporarily discontinuing hGH treatment; the 'off hGH' study for Group II was performed before they were begun on hGH. Informed consent was obtained from patients and their parents. The studies were approved by the Human Experimentation Committee at the University of Michigan.

Basal gonadotrophins and gonadotrophin responsiveness to iv synthetic GnRH (2.5 µg/kg, Parke Davis No. CI-785) were determined on the morning of the first day of each hospital admission using a standardized test and standard methods for radioimmunoassay of LH and FSH as previously described (Kelch et al. 1976).

Table 1.
Effects of GH-treatment on pituitary responsiveness to iv GnRH and Leydig cell responsiveness to hCG.

Pt.	CA (years)	BA (years)	Trophic hormone deficiencies	GnRH response Δ max. * (mIU/ml)				Serum Testosterone (ng/ml)			
				LH		FSH		Off GH		On GH	
				Off	On	Off	On	Basal	Max	Basal	Max
1	10 3/12	6 0/12	GH	7.8	11.2	4.8	2.7	< 0.2	3.2	< 0.2	2.6
2	17 1/12	14 9/12	GH, TSH	1.7	2.0	1.9	1.8	< 0.2	1.3	< 0.2	0.7
3	23 6/12	13 6/12	GH, TSH, ACTH	1.0	1.7	0.7	1.1	< 0.2	2.8	< 0.2	2.2
4	8 10/12	3 6/12	GH, TSH, ACTH	2.8	3.2	0	1.2	< 0.2	3.6	< 0.2	4.3
5	11 2/12	8 0/12	GH	10.7	5.1	3.0	2.1	< 0.2	1.3	< 0.2	1.7
6	11 6/12	4 0/12	GH, TSH, ACTH	1.5	0.5	4.8	0.8	< 0.2	1.3	< 0.2	---
7	7 7/12	5 0/12	GH	4.9	2.2	16.4	9.2	< 0.2	1.2	< 0.2	1.4
Mean rise \pm SE				4.3 \pm 1.4	3.7 \pm 1.4	4.5 \pm 2.1	2.7 \pm 1.1	2.1 \pm 0.4		2.2 \pm 0.5	
Short normal boys (n = 22) (BA 2-10 years)				7.4 \pm 0.7	7.1 \pm 1.1						
Normal pre-pubertal boys ⁺ (n = 8) (mean \pm SE)				3-19**	1-19**						
						Basal		Max		Max	
						0.2 \pm 0.1		1.7 \pm 0.3			

* Δ Max = maximum rise of LH/FSH from mean of control values. + Winter et al. (1972). ** Range. ° Sample lost due to laboratory error.

Each subject received 200 IU of hCG (Ayerst) im at 12.00 h Day 1 (Tuesday) and at 09.00 h for 2 additional consecutive days during each admission. Blood was drawn at 08.00 h on each hospital day. The 08.00 h testosterone concentration of day 1 was used as baseline. All samples were frozen at -20 C until analysis. Testosterone determinations were performed in a single double antibody radioimmunoassay (Ismail et al. 1972). Results are expressed as the maximum concentration achieved. Student's paired *t*-test was used for statistical comparisons.

Results

Prior to treatment the mean yearly linear growth velocities of Group I and Group II were 2.9 and 2.3 cm/year, respectively. Mean linear growth velocity during the first treatment year for Group I was 8.4 cm/year and during the year of the study were normal for the patient's ages. The mean linear growth for Group II for the first year of treatment was 7.1 cm. Basal serum LH and FSH concentrations off and on hGH therapy were not significantly different. Basal LH values were 3.4 ± 0.5 ($X \pm SE$) mIU/ml off GH and 3.2 ± 0.5 mIU/ml on GH therapy. Basal FSH values off GH were 1.7 ± 0.2 and on GH were 1.6 ± 0.2 mIU/ml. LH responses to iv GnRH in patients 2,3,4,6 were considerably below the mean and outside the range of responses found in short normal boys with bone ages less than 10 years (Table 1). These 4 patients also had multiple anterior pituitary hormone deficiencies and probably have gonadotrophin deficiency.

The maximum serum testosterone concentration occurred 72 h after beginning daily hCG injections, while on or off hGH, in all but one instance. The maximum value on hGH therapy occurred at 24 h for patient 6. There was no significant difference between mean testicular responses of the off treatment and on treatment periods (Table 1). Responses to hCG did not correlate with basal serum concentrations of LH or FSH, or responses to iv GnRH.

Discussion

This study failed to demonstrate a GH induced change in the testosterone responsiveness to hCG stimulation in pre-pubertal boys with hypopituitarism. The observed responses are within the normal range of values found in normal boys ages 5–14 years as reported by Winter et al. (1972) after an identical test. No discernable effect was observed either in patients who had not received previous growth hormone treatment or in patients in whom growth hormone therapy had been discontinued transiently.

The clinical evidence which suggests that growth hormone might potentiate LH/hCG stimulation of Leydig cells includes the observations that male infants with hypopituitarism often have microgenitalia at birth (Lovinger et al. 1975), and individuals with GH deficiency generally have delayed puberty (Goodman et al. 1968). Furthermore, small genitalia in adult men who have isolated GH deficiency has been thought to be secondary to growth hormone effects upon Leydig cell function (Laron & Sarel 1970). Finally, Zachman (1975) studied the effects of hGH therapy on testicular response to hCG in a 23 year old man who had a history of normal puberty but had familial isolated hGH deficiency. That patient's testosterone response to hCG before hGH treatment was subnormal, but after receiving hGH for 3 months his response was normal.

Knowledge of the effects of growth hormone on Leydig cells is limited. Yang et al. (1974) observed that mouse Leydig cell tumour growth is enhanced by growth hormone. Bex & Bartke (1977) have recently reported that growth hormone treatment in the hamster is capable of reversing the decline in testicular LH binding capacity induced by short photoperiods. In addition, we and others have demonstrated that ovine growth hormone partially prevents the loss of testicular LH/hCG receptors and loss of testicular testosterone response to LH that occurs in adult rats after hypophysectomy (Zipf et al. 1977; Odell & Swerdloff 1976; Zipf et al. 1978; Zipf & Berntson 1981). These observations suggest a prominent role for growth hormone in adult Leydig cell function.

The dose of hGH used in this study was sufficient to maintain or establish linear growth rates equal to or greater than normal for the patients' skeletal ages. However, it is possible that larger doses of hGH may have resulted in a positive effect on testicular responsiveness. It is equally possible that an effect of hGH may only be apparent when there are a large number of highly stimulated and well differentiated Leydig cells. This occurs during the foetal period associated with sexual differentiation and re-occurs again in late puberty. Gonadotrophin deficiency might affect responses, but no differences were noted between boys with isolated hGH deficiency and multiple pituitary hormone deficiencies. An effect of maturity or prior stimulation is the most likely explanation of the discrepancies between our study and the observations of Zachman (1975), and suggests GH effects on Leydig cell function may be synergistic with the gonadotrophins in man.

Recently Sizonenko et al. (1977) have reported a positive correlation between testicular response and basal serum FSH concentrations in 16 pre-pubertal boys with hypopituitarism given a total of 9000 IU hCG over 12 days. This was not seen in our study, but the limited number of patients in this study, together with the marked variability in basal FSH concentrations prevents us from making any conclusions regarding this relationship. Growth hormone treatment was not associated with a consistent effect on either basal serum concentrations of LH and FSH, or on LH and FSH responses to GnRH. These findings are similar to our previous investigation (Kelch et al. 1976).

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