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G Tolis, A Mehta, A M Comaru-Schally, A V Schally

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Research Article

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Suppression of Androgen Production by D-Tryptophan-6-Luteinizing Hormone-releasing Hormone in Man

G. TOLIS, A. MEHTA, A. M. COMARU-SCHALLY, and A. V. SCHALLY,
Departments of Medicine, Obstetrics and Gynecology, Royal Victoria Hospital, Quebec H3A 1A1, and McGill University School of Medicine, Quebec H3G 1Y6, Canada; Veterans Administration Medical Center and Tulane University School of Medicine, New Orleans, Louisiana 70140

ABSTRACT Four male transexual subjects were given a superactive luteinizing hormone-releasing hormone (LHRH) analogue, D-tryptophan-6-LHRH at daily doses of 100 μg for 3–6 mo. A decrease in beard growth, acne, and erectile potency was noted; the latter was documented objectively with the recordings of nocturnal penile tumescence episodes. Plasma testosterone and dihydrotestosterone levels fell to castrate values; basal prolactin and luteinizing hormone levels showed a small decline, whereas the acutely releasable luteinizing hormone was significantly suppressed. A rise of plasma testosterone from castrate to normal levels was demonstrable with the use of human chorionic gonadotropin. Discontinuation of treatment led to a normalization of erectile potency and plasma testosterone. The suppression of Leydig cell function by D-tryptophan-6-LHRH might have wide application in reproductive biology and in endocrine-dependent neoplasia (where it could replace surgical castration).

INTRODUCTION

Stimulation of pituitary-gonadotropin and testicular steroid production follows the acute administration of luteinizing hormone-releasing hormone (LHRH)[1] or its agonistic analogues in experimental animals and human beings (1–5). A paradoxical decrease in gonadal steroid output, however, has been reported in animals treated chronically with large doses of superactive LHRH analogues (6–8).

To evaluate whether analogous phenomena can occur in man, we measured plasma testosterone, dihydrotestosterone, and estradiol after the chronic administration of D-tryptophan (Trp)-6-LHRH in four male transexuals before removal of the testes, as part of their sex reassignment. Our findings are reported here.

METHODS

Four male transexual subjects 19–29 yr old agreed to participate in the study. These patients had a long waiting period before surgery (testicular removal and creation of vagina); in the interim they were undergoing extensive psychiatric evaluation. To nullify their objectionable male signs, like nocturnal erections and facial hair growth, so that they could identify more closely with their preferred gender, they were referred to us for "hormonal treatment." This is usually accomplished with castration and the administration of estrogens. It was explained to the subjects that functional castration could be achieved with the use of the LHRH analogue. They all accepted the proposal and signed an informed consent.

Measurements of serum follicle-stimulating hormone (FSH) (9), luteinizing hormone (LH) (9), prolactin (PRL) (10), testosterone (T) (11), dihydrotestosterone (DHT) (12), and estradiol (E2) (11) were done with standard radioimmunoassay methods. For the assessment of acutely releasable pituitary gonadotropin, FSH and LH serum levels were measured before and at 2-h intervals for 6 h after the subcutaneous injection of 100 μg D-Trp-6-LHRH-A. For the assessment of the quality and quantity of nocturnal erections, we monitored the nocturnal penile tumescence (NPT) episodes via a plethysmographic recorder (Event Systems Inc., N. J.). After basal values were obtained treatment was started. Synthetic D-Trp-6-LHRH was administered daily for 3–6 mo. Subjects A, B, and C received 100 μg daily by

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Address requests for reprints to Dr. George Tolis, Royal Victoria Hospital, Montreal, Quebec H3A 1A1.

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[1] *Abbreviations used in this paper*: DTH, dihydrotestosterone; E2, estradiol; FSH, follicle-stimulating hormone: LH, luteinizing hormone: LHRH, luteinizing hormone-releasing hormone: NPT, nocturnal penile tumescence: PRL, prolactin: T, testosterone: D-Trp-6-LHRH, D-tryptophan-6-LHRH.

subcutaneous injections; subject D received 500 μg daily intranasally. Recording NPT was repeated on and off treatment in two subjects. Hormonal levels were measured at regular intervals during the treatment period. In subjects A and B, and LHRH-A test was done before and on the 8th wk of the treatment with the analogue. 1 wk before discontinuation of the treatment, the ability of the Leydig cells to respond to human chorionic gonadotropin (A.P.L., Ayerst Laboratories, Montreal, Canada) was tested. 5,000 IU/m² were administered intramuscularly and plasma T was measured daily for 4 d as previously described (13).

RESULTS

Clinical. All transexual subjects noticed a decrease in the rate of facial hair growth which resulted in a change in the frequency of shaving or electrolysis. In addition, they described themselves as more calm and experiencing erections far less frequently. In particular, subjects A, B, and C experienced no erections after the 3rd wk of treatment.

Hemodynamic. NPT studies were done on two subjects. In both, a decrease in the amplitude and frequency of nocturnal erections was seen. Data on subject A is shown in Fig. 1. Although there was no change in the total sleep time during or off treatment with the D-Trp-6-LHRH, there was a suppression in the fraction of time of sleep spent in tumescence (10.4 vs. 27.6%), there were fewer episodes of erections, and the attained penile diameter was below 1 cm as contrasted to a mean of 2.8 cm during the control period. The suppression of NPT episodes was seen at the time of low circulating plasma T (Fig. 1).

Hormonal. Basal values for FSH, LH, PRL, T, DHT, and E2 were within normal range for all subjects (Table I). Similarly, peak LH values increased three- to fivefold after the acute administration of LHRH in the two subjects tested (Fig. 2). Plasma sex steroid concentrations fell by the 1st wk of treatment, reached very low levels by the 4th wk of treatment, and remained in this castrate range thereafter in the subjects treated by subcutaneous injections. In subject D treated by intranasal application, the decline was slower and levels never reached castrate values (Table I). A decline in PRL was seen in those subjects in whom T and E2 levels became very low. Basal serum FSH was unchanged but serum LH showed a small decline in basal values; a substantial decrease in the peak LH levels after LHRH-A was noticed at the 8th wk of therapy with the analogue (Fig. 2). The ad-

	SUBJECT B	
TREATMENT	**D-TRP6-LHRH**	**OFF TREATMENT**
DATE	**15/3/80**	**21/4/80**
TOTAL SLEEP TIME (min)	**450**	**525**
NUMBER OF TUMESCENCE EPISODES	**2**	**9**
TIME SPENT IN TUMESCENCE (min)	**22 min**	**15 min**
PENILE EXPANSION (cm)	**0.5-1.0 cm**	**0.5-1.0 cm**
	25 +	**20**
	0.5-1.0	**1.5-2.0**
		35
		3.0-3.5
		20
		2.0-2.5
		20
		3.0-3.5
		10
		2.5-3.0
		15
		2.0-2.5
		5
		1.5-2.0
		5 +
		2.0-2.5
TOTAL	**47 min = 10.4 %**	**145 min = 27.6 %**
		
PLASMA TESTOSTERONE	**<0.1ng/ml**	**5.83ng/ml**

FIGURE 1 Note the suppression of plasma testosterone (0.1 ng/ml) and the decrease in the frequency and amplitude of episodes of NPT during treatment with D-Trp-6-LHRH and its normalization 5 wk after discontinuation of treatment (right panel).

TABLE I

Clinicolaboratory Data on Four Transexual Male Subjects Treated Chronically with D-*Trp-6-LHRH*

Subjects	A	B	C	D
Age, *yr*	29	19	20	28
Daily dose, *μg*	100	100	100	500
Route	SC*	SC	SC	IN
Duration, *mo*	6	3.5	3	2
T, *ng/ml*				
Basal	5.3	5.4	6.8	12.9
2-wk treatment	1.5	2.5	0.9	2.7
End of treatment	0.3	ND	0.11	1.01
DHT, *ng/ml*				
Basal	0.63	0.61	—	0.99
8 wk	ND	ND	—	0.32
LH, *ng/ml*				
Basal	30	57	33	20
End of treatment	22	35	24	16
E2, *pg/ml*				
Basal	15	20	30	—
End of treatment	ND	ND	ND	—
PRL, *ng/ml*				
Basal	16.6	22.0	17	11
End of treatment	5.8	5.8	8	14
FSH, *ng/ml*				
Basal	99	93	60	115
End of treatment	150	43	129	45

Normal values (range): T, 2–8 ng/ml; DHT, 0.2–2.0 ng/ml; LH, 30–200 ng/ml; FSH 60–300 ng/ml; E2 10–40 pg/ml; PRL 3–25 ng/ml.

* SC, subcutaneous; IN, intranasal; ND, not detectable.

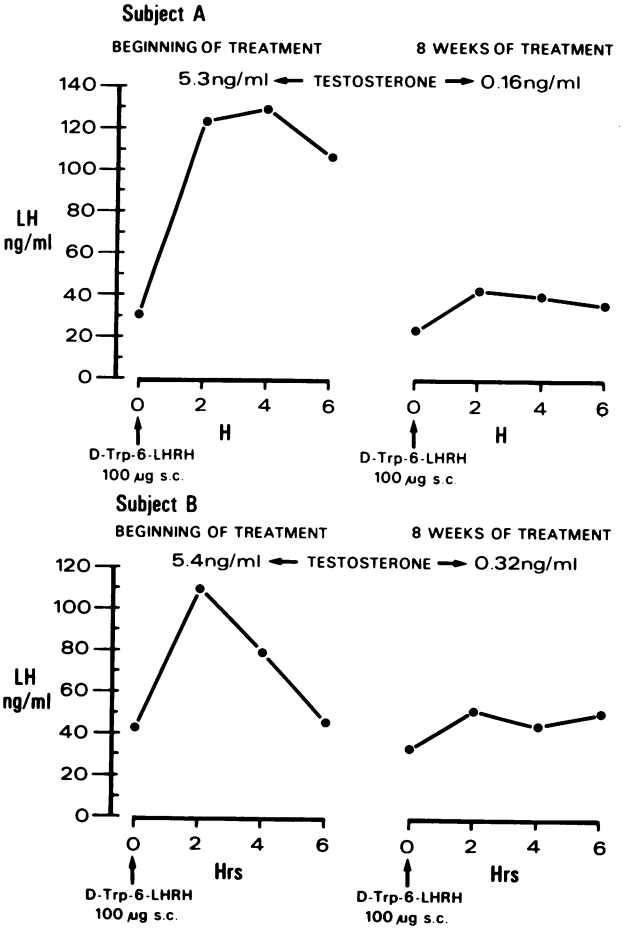

FIGURE 2 Suppression of basal plasma T and acutely releasable LH in two transexual subjects during chronic administration of D-Trp-6-LHRH.

ministration of human chorionic gonadotropin resulted in a prompt increase in plasma T to levels similar to those before initiation of therapy with D-Trp-6-LHRH; the peak values, obtained for subjects A and B, were 5.85 and 6.2 ng/ml, respectively.

DISCUSSION

Our data indicate that chronic administration of large doses of D-Trp-6-LHRH suppresses the testicular production of T. The decrease in the frequency and quality of the NPT episodes during the treatment with the LHRH analogue and the re-establishment of normality (14, 15) after the discontinuation of the treatment, at the time when plasma T levels had returned to normal, strongly indicates that the decrease in erectile potency was not psychogenic but most likely due to hypoandrogenemia. (14–16). The normal (and falling) PRL levels during therapy with D-Trp-6-LHRH speak against a role of hyperprolactinemia in the suppression of Leydig cell function (13, 17). It is possible that the decline of serum PRL was secondary to the observed fall of plasma sex steroids and in particular E2. The decline in basal serum LH and in the pituitary gonadotrope responsiveness to LHRH-A as well as the normalization of plasma T after human chorionic gonadotropin administration indicates that a pituitary-dependent mechanism participates in suppression of plasma T; however, some direct effect of D-Trp-6-LHRH upon the Leydig cells may be considered, in view of the fact that a significant fall of plasma T occurred by the 1st wk, an unlikely event even after hypophysectomy (unpublished observations). Irrespective of the mechanisms, these findings may have far reaching implications. For instance, D-Trp-6-LHRH could be considered for the suppression of cancer growth in sex steroid-dependent tumors (breast and prostate), reduction of oversexuality in sex offenders and nymphomaniacs, and arrest of precocious puberty (18). On the other hand, because of its powerful inhibitory effect on T and DHT levels with ensuing Fall in libido and potency, the use of such LHRH analogues may not constitute the most appropriate

approach for suppression of gametogenesis and use as a male "contraceptive." Future work using different regimens of LHRH analogues alone or in combination with other drugs may shed more light on some of the possible applications of the LHRH analogues for these purposes.

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