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The 24-Hour Secretory Pattern of LH and the Response to LHRH in Transsexual Men

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Ten separate aspects of hypothalamic and pituitary function were studied in 13 male-to-female transsexuals and compared to the results of 7 heterosexual adult men. In 4 of 5 transsexuals, the 24-hour mean serum concentration of LH, the LH pulse frequency or amplitude, or the apparent half-life of disappearance of serum LH were greater than the 95% confidence limit of normal men. The maximum concentration of LH or FSH following the administration of 100 μg LHRH, the area under the response curve of LH or FSH following LHRH, or both were significantly greater than normal in 5 of 13 male-to-female transsexuals. The response of LH following the administration of LHRH was repeated in 3 subjects during estrogen therapy, and in one there was a paradoxical increase in the response of LH. Transsexualism may be associated with a neuroendocrine defect in the hypothalamus or pituitary that is characterized by high-frequency, high-amplitude pulsatile secretion of pituitary LH.

KEY WORDS: transsexualism; hypothalamus; pituitary; LHRH; luteinizing hormone; follicle stimulating hormone.

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INTRODUCTION

Male-to-female transsexuals have a persistent desire to be women in manner, dress, and behavior. This desire is manifested by negative feelings toward their external genitalia, by their intent to have gender reversal surgery, and by a lack of interest in heterosexual relationships since their own gender identity is opposite to that dictated by the presence of male external and internal genitalia (Feighner *et al.*, 1972). From the work of Jost (1971), a concept of male sexual differentiation has evolved. The presence of a Y chromosome induces formation of testes that elaborate testosterone during fetal life. As a consequence of fetal testicular testosterone secretion, the Wolffian ducts develop into the epididymides, vasa deferentia, seminal vesicles, and prostate gland. In the bipotential external genital anlage, testosterone from fetal testes is converted to dihydrotestosterone, which causes the external genitalia to differentiate into male structues.

In this model, no mechanism is considered for the final expression of male sexual differentiation – the psychological perception of gender identity by the individual. We considered the possibility that some biochemical or physiological abnormality exists to explain the dichotomy between genetic, gonadal, and genital sex and the opposing gender identity in male-to-female transsexuals. Peptide hormones have been associated with changes in sexual behavior (Moss, 1979; Lipton *et al.*, 1976; Evans and Distiller, 1979; McAdoo *et al.*, 1978). The anatomy of the hypothalamus of male rats is different than that of female rats (Raisman and Field, 1971). Although the content of gonadotropin releasing hormone (LHRH) in the hypothalamus of human fetuses is similar in both sexes, the pituitary content of LH and FSH is greater in female fetuses by 10-14 weeks of gestation, a difference that persists throughout gestation (Kaplan *et al.*, 1976). In adults, the pituitary response to LHRH is greater in women, and the response depends on the stage of the menstrual cycle (Jaffe and Keye, 1974; Mecklenburg and Sherins, 1974). Based on these observations of sex differences in pituitary function during embryonic life that may presage differences between adult men and women, we measured certain aspects of hypothalamic and pituitary function in 13 transsexual men.

SUBJECTS

Clinical features of the 13 subjects of this study are summarized in Table I. Each subject fulfilled the criteria for transsexualism defined by Feighner *et al.* (1972). All of the subjects considered themselves to be females "trapped in a man's body" and usually had perceived this since early

Table I. Clinical Features of Transsexual Men

Subject	Age (years)	Height (cm)	Weight (kg)	Testicular volume[a]	Sperm count (million/cc)
A	27	172	58.3	20	–
B	29	180	81.5	30	123.0
C	18	165	64.0	40	1.9
D	17	186	60.0	30	–
E	28	168	62.6	40	90.0
F	19	175	121.0	–	97.0
G	23	178	54.4	40	1.0
H	22	173	63.8	50	16.0
I	25	175	60.2	35	0
J	24	165	61.0	50	14.0
K	27	173	72.4	22	–
L	20	188	63.5	40	–
M	17	175	53.6	27	–

[a]Includes both testes; normal combined volume is 30-50 cc.

childhood. All of the subjects dressed as females, and most did so in public all the time. None of the subjects had undergone genital surgery. Most subjects were actively participating in group psychotherapy in anticipation of sex reassignment surgery. All of the subjects except subject A were studied before beginning oral estrogen therapy. Subject A had taken a conjugated estrogen for 6 months but had stopped 3 months before he was studied. He had 5 cc of glandular tissue in each breast. None of the other subjects had gynecomastia. Serum estrone and estradiol concentrations were normal at the time of these studies (Aiman and Boyer, 1982). Since any estrogen taken by these subjects would increase the serum concentrations of estrone or estradiol, normal serum concentrations provide evidence that the subjects were not taking estrogen. Sperm counts in semen samples collected by masturbation were low in 5 of 8 subjects (C, G, H, I, and J). This was verified by repeating the semen analyses at least once for each of these subjects. None of the subjects admitted to elevating their testes into the inguinal canals, and all had scrotal testes at the time of examination. Sperm motility and morphology were normal in those men who had sufficient sperm to assess these parameters. Since serum concentrations of estrone and estradiol were normal (data not shown), the low sperm counts were not the consequence of surreptitious use of exogenous estrogen.

METHODS

Each of the subjects was studied at the General Clinical Research Center of the University of Texas Southwestern Medical School after con-

senting to a protocol approved by the Human Research Review Committee. Following a night in the Clinical Research Center, an indwelling catheter was inserted into an antecubital vein at 8:00 a.m., and blood was withdrawn every 20 minutes thereafter for 24 hours. The serum was separated and frozen until all 72 samples from each subject were assayed together for LH (Boyar *et al.*, 1972b). Four normal heterosexual adult men (ages 17-26) were studied in an identical manner, and results have been published (Boyar *et al.*, 1978). In this assay, 1 ng LER 907 is equivalent to 0.323 mIU LH and 0.059 mIU FSH.

The 24-hour mean concentration of LH and the number of LH secretary pulses were computed. An LH secretary pulse occurred when an LH concentration exceeded the preceding value by 20%, a value that is outside the range of intra-assay variability (5-7%). The amplitude of each LH pulse was calculated as the difference between the peak and baseline values. The apparent half-life of disappearance of serum LH (T½) was computed from the slope of the decline in the natural log concentration of each LH peak (Gurpide, 1975). The peak LH concentration and the next 3 concentrations were used to compute the T½. Thus, the immediate disappearance was calculated. After 40 to 60 minutes, the slope becomes nonlinear and the computed T½ becomes a composite of peripheral metabolism and pituitary secretion of LH.

The response to 100 μg of LHRH[5] administered intravenously was examined by measuring the concentration of LH and FSH (Boyar *et al.*, 1973) in serum obtained 15, 30, 45, 60, 90, 120, 150, and 180 minutes after the LHRH injection. These data were compared to those of seven normal heterosexual men studied in an identical manner. The baseline value of LH and FSH was the mean value from the samples measured over 24 hours or the average concentration in serum obtained 30 minutes and 15 minutes before injecting the LHRH. Two aspects of the response to LHRH were examined. First, the difference between the maximum concentration and baseline concentration of LH and FSH was calculated. Second, the area under the curve of concentration (LH or FSH) plotted against time after LHRH injection was measured.

The response to a 100-μg injection of LHRH was studied a second time when subjects B, C, and E had taken 50 μg of ethinyl estradiol daily for 3 months. This was done because Seyler and co-workers reported this aspect of pituitary function to be the only discernible abnormality in 9 female transsexuals (Seyler *et al.*, 1978). None of the heterosexual men were studied during estrogen treatment.

Ten separate aspects of hypothalamic-pituitary function were examined, and these are listed in Table II with a summary of abnormal

[5]Provided by Ayeast Laboratories.

Table II. Abnormal Findings in Transsexual Men

Measurement	Subjects with abnormalities											
	A	B	C	D	E	F	G	H	I	J	K	L	M
Mean LH (mIU/ml)	a		c		e		g		i		k		
LH pulse frequency (#/24h)[a]	a	b											
LH pulse amplitude (mIU/ml)[a]			c		e								
T½ of serum LH (minutes)			c										
LH response to LHRH (mIU/ml)	a		c		e						k		
Area of LH response curve	a		c								k		
Mean FSH (mIU/ml)									i				
FSH response to LHRH (mIU/ml)	a		c						i		k		
Area of FSH response curve	a		c								k		
Effect of estrogen		b											

[a]Not examined in subjects F through M.

findings in these male-to-female transsexuals. Any value was considered abnormal if it differed by two standard deviations or more from the corresponding mean value of normal men.

RESULTS

In subjects A-E, the 24-hour mean concentration of LH was 9.0-16.6 mIU/ml with a group mean of 12.0 mIU/ml (Table III). This was not significantly greater than the mean value of 8.8 mIU/ml in four heterosexual men, although the 24-hour mean LH concentration of subjects, A, C, and E exceeded the mean value of normal men by more than 2 standard deviations. The baseline concentration of LH in subjects G, I, and K (Table IV) also exceeded the 95% confidence limit of these 4 normal men.

The LH pulse frequency or amplitude was abnormally high in subjects A, B, C, and E, although the mean values of all transsexual men were not significantly greater than normal. The apparent half-life of disappearance of LH from serum was marginally high only in subject C, whereas the mean value for all transsexual men was normal.

The response of LH and FSH to 100 μg LHRH is illustrated in Fig. 1. Although the response of both gonadotropins was greater in the transsexual subjects, none of the differences in mean values were significant. However, the maximum response of LH in subjects A, C, E, and K exceeded the mean value of normal men by more than 2 standard deviations. The area under the LH response curve was high in subjects A, C, and K (Table IV).

The maximal response of FSH to LHRH and the area under the response curve was also abnormal in subjects A, C, and K. The baseline concentration of FSH was high in subject I, as was the maximum response to LHRH.

Table III. 24-hour Secretory Dynamics of LH in Five Transsexual Men

Subject	24-hour mean LH (mIU/ml)	Pulse frequency (no./24 hour)	Pulse amplitude (mIU/ml)	Pulse amplitude (% increase)	T½ of LH[a] (minutes)
A	16.6	11	6.6 ± 0.9[b]	88.7 ± 16.8	84.8 ± 8.2
B	9.4	11	5.6 ± 0.9	89.9 ± 11.9	90.2 ± 9.8
C	13.3	9	11.6 ± 4.9	130.8 ± 49.8	121.0 ± 33.5
D	9.0	9	4.9 ± 0.8	66.9 ± 10.2	111.3 ± 13.9
E	11.8	7	9.0 ± 3.8	100.7 ± 39.7	90.0 ± 7.4
Mean ± SE	12.0 ± 1.4	9.4 ± 0.8	7.5 ± 1.2	95.4 ± 10.4	99.6 ± 15.6
Normal men[c] ($n = 4$)	8.8 ± 0.4 $p > 0.05$	8.2 ± 0.4 $p > 0.05$	4.3 ± 0.8 $p > 0.05$	59.3 ± 11.3 $p > 0.05$	84.8 ± 9.0 $p > 0.05$

[a]Apparent half-life of serum LH computed from the rate of disappearance of each peak concentration.
[b]Mean ± SE.
[c]See Boyar *et al.* (1978), Boyar *et al.* (1978b).

Table IV. Response of LH and FSH to LHRH[a]

	LH			FSH		
Subject	Baseline (mIU/ml)	Peak concentration (mIU/ml)	Area of response curve (mIU-h/ml)	Baseline (mIU/ml)	Peak concentration (mIU/ml)	Area of response curve (mIU-h/ml)
A	16.6	95.3	130	15.3	32.8	86
B	9.4	49.3	94	13.4	20.1	55
C	13.3	136.5	198	15.8	51.0	115
D	9.0	18.4	42	4.6	6.1	18
E	11.8	92.3	104	6.7	18.1	45
F	10.3	35.5	70	7.5	12.9	34
G	12.3	27.4	50	9.9	12.5	35
H	7.8	21.1	34	9.6	12.8	34
I	16.3	45.1	90	18.7	30.3	80
J	8.2	46.1	72	10.0	17.0	45
K	12.0	291.3	327	11.9	57.1	136
L	8.2	51.8	68	5.9	8.6	17
M	10.3	56.00	90	10.6	14.2	40
Mean ± SE	11.2 ± 0.8	74.3 ± 20.3	105 ± 22	10.8 ± 1.2	22.6 ± 4.4	57 ± 21
Normal Men ($\bar{x}$ ± SE)	10.4 ± 0.9	40.7 ± 6.2	66 ± 9	11.1 ± 1.4	16.3 ± 2.3	45 ± 7

[a]None of the differences is statistically significant.

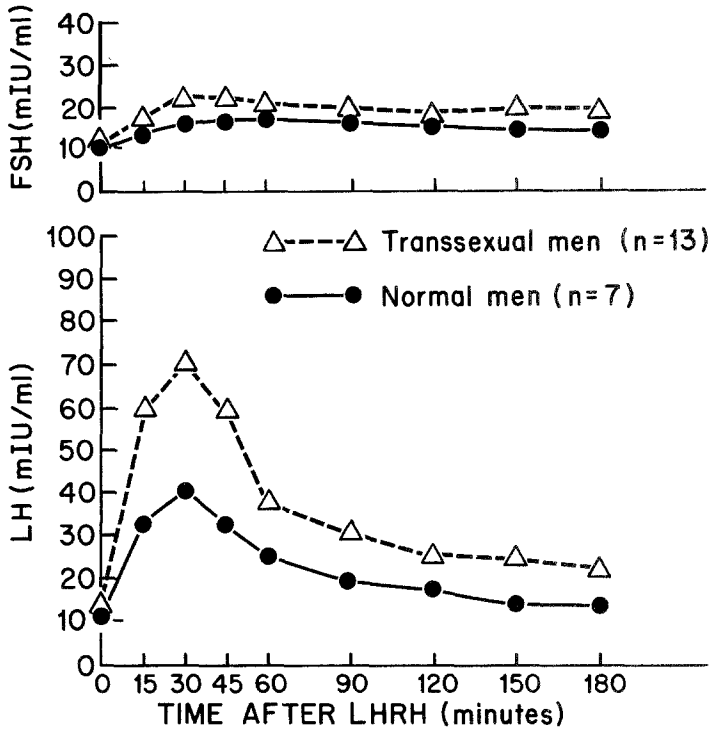

Fig. 1. 100 μg LHRH was administered intravenously at time 0. At no time are the differences between normal and transsexual men significant.

Subjects B, C, and E were studied after they had taken estrogen for at least 3 months. In subject B, treatment with ethinyl estradiol caused an augmented LH response to LHRH (Fig. 2). In normal men (Santen, 1975) and in subjects C and E (Fig. 2), LH response to LHRH was reduced during estrogen treatment.

In summary, some aspect of LH and FSH secretory dynamics was abnormal in 7 of 13 transsexual men (Table II). A single abnormality was present in subject G. In all other subjects with some abnormal response, there were 2 to 7 abnormalities present. Moreover, the abnormality observed was always an increase above the 95% confidence limit of normal men.

DISCUSSION

Secretion of LH is characterized by noncyclic pulsatile bursts superimposed on a tonic baseline. Since pituitary portal venous (Carmel *et al.*,

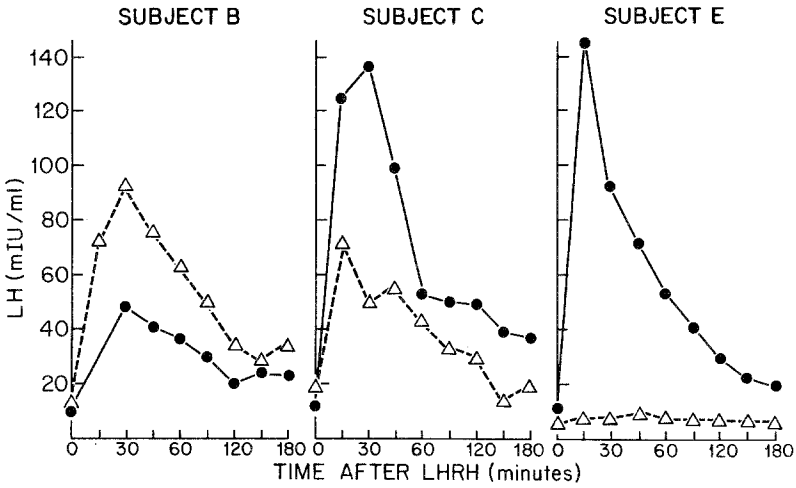

Fig. 2. ●——●, response to LHRH before estrogen therapy; Δ---Δ, response to LHRH after 3 months of ethnyl estradiol. In subject B, LH concentrations increased during estrogen therapy, whereas a normal response (Santen, 1975) was observed in subjects C and E.

1976) and peripheral concentrations (Seyler and Reichlin, 1974a) of LHRH also fluctuate in a similar manner, the changes in serum LH concentration probably reflect changes in pituitary secretion in response to hypothalamic LHRH. Changes in the peripheral metabolism of LH are probably not important because the rate of disappearance or the metabolic clearance rate of LH does not differ in a wide variety of conditions (Santen and Bardin, 1973; Ross *et al.*, 1970). Baseline LH concentrations, the frequency of LH secretory pulses, the amplitude of these pulses, and the apparent half-life of LH in plasma are similar in adult men and preovulatory women (Boyar *et al.*, 1972b; Rubin *et al.*, 1972; Nankin and Troen, 1971, 1972; Naftolin *et al.*, 1972; Yen *et al.*, 1972a; Midgley and Jaffe, 1971).

Since the apparent half-life of LH was normal in 4 of 5 transsexual men, the observed abnormalities in LH secretion are most likely the result of abnormal hypothalamic secretion of LHRH. The abnormality is characterized by a high-frequency and high-amplitude response of pituitary LH.

If this interpretation of an abnormal pattern of hypothalamic LHRH secretion is correct, then three questions arise. First, are the observed abnormalities the cause of transsexualism? Nankin and co-workers (1977) have demonstrated increased FSH concentrations and an augmented response to 100 μg of LHRH in infertile men with a variety of disorders. Snyder and co-workers (1977) have reported supranormal FSH responses to LHRH in oligospermic men. The abnormalities in the transsexual men were not limited to those with small testes or defective spermatogenesis, so it is

not probable that the changes are due to testicular failure. Moreover, testicular steroidogenesis was normal in these men (Aiman and Boyar, 1982).

Second, what can modify hypothalamic function in such a way that the observed response of LH in the transsexual subjects would result? Testosterone and estrogen depress basal levels of LH as well as the frequency and amplitude of LH pulses (Santen, 1975; Stewart-Bentley *et al.*, 1974; Yamaji *et al.*, 1972). Conversely, baseline and pulsatile levels of LH are increased in subjects with absent androgen action (Boyar *et al.*, 1978; Root et al., 1972) and in agonadal or postmenopausal women (Yen *et al.*, 1972b; Root *et al.*, 1972). Seyler and Reichlin (1974b) have demonstrated increased LHRH concentrations but decreased LH concentrations following estrogen administration to men. This is suggestive that estrogens stimulate hypothalamic release of LHRH but simultaneously suppress the pituitary secretion of LH. Dörner (1978) has proposed that androgen deficiency in genetic males during a critical period of brain development gives rise to female brain differentiation. Androgen and estrogen dynamics, however, were found to be normal in these transsexual subjects (Aiman and Boyar, 1982).

If the observed abnormalities in LHRH effect are significant, then what are the behavioral sequelae of these abnormalities? Pituitary hormones can modify learning (Lande *et al.*, 1973), and hypothalamic hormones are associated with a variety of behavioral traits (Moss, 1979; Ungar, 1975; Lipton *et al.*, 1976) including sexual behavior (Moss *et al.*, 1979; Pfaff, 1973; Moss and McCann, 1973; Gessa *et al.*, 1979). These changes may be related to a diminished frequency of electrical discharge observed in LHRH-responsive neurons (Renaud *et al.*, 1975). The finding of an abnormal secretory pattern of LH in 7 of 13 of the transsexual subjects is consistent with the hypothesis that the gender dysphoria in these men may also be the consequence of an abnormality in hypothalamic LHRH. Although these data are consistent with this view, they do not provide conclusive evidence to establish this hypothesis.

In summary, some abnormality of hypothalamic-pituitary function was noted in the majority of transsexual men studied, before they began estrogen therapy. Since none of the mean values of transsexual men were significantly greater than those of normal men, the significance of these findings is not certain. These data, however, are consistent with the view that the abnormality observed in the majority of transsexual men may reflect a biochemical or neuroendocrine defect within the brain that is associated with transsexualism.

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