Effect of thyrotrophin-releasing hormone on serum prolactin levels in men with azoospermia

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Summary. Infertile men with azoospermia and low testosterone levels because of Klinefelter's or Sertoli cell-only syndrome responded to a single injection of TRH by an increase in serum prolactin levels. The degree of this response was not as great as in fertile men with normospermia and normal testosterone levels, although initial prolactin levels had been similar in both groups. The results demonstrate a link between testosterone and prolactin levels in fertile and infertile men.

The role of prolactin in the physiological processes of male mammals is unclear. Prolactin has been reported to induce activity of the hydroxysteroid dehydrogenase enzymes that are required for testosterone metabolism (Evans, 1962; Bartke & Lloyd, 1970; Hafiez, Philpott & Bartke, 1971) and to be involved in maintaining some of the hormone precursors for LH stimulation of testosterone synthesis (Hafiez, Lloyd & Bartke, 1972; Musto, Hafiez & Bartke, 1972). However, no significant differences in the serum prolactin levels of normo- and azoospermic men were noticed (Sheth, Joshi, Moodbidri & Rao, 1973), although the testosterone concentrations in such men were presumably very different (Hudson, Burger, de Kretser, Coghlan & Taft, 1970).

Contradictory findings have been reported for serum prolactin levels in patients with Klinefelter's syndrome: Hagen, McNeilly, Arroe, Emmersten & Froland (1974) found no differences in serum prolactin levels between patients with this syndrome and those with normal numbers of spermatozoa, while Aubert, Arroyo, Detolle & L'Hermite (1973) reported higher serum prolactin levels in one male with Klinefelter's syndrome than in normospermic men.

Thyrotrophin-releasing hormone (TRH) is known as a potent stimulator of prolactin release from the pituitary (Rakoff, Vandenberg, Siler & Yen, 1974), and it has been suggested that prolactin synthesis might also be affected (L'Hermite *et al.*, 1972; Kaplan, Grumbach & Friesen, 1972). A difference between the mean peaks of prolactin response following TRH administration before and after testosterone administration was demonstrated by Burman *et al.* (1975) for patients with Klinefelter's syndrome who had normal testosterone levels before treatment, suggesting an over-responsiveness to TRH.

We decided, therefore, to investigate the possible correlation between serum testosterone levels, prolactin levels and sperm count, and to study prolactin release in men with different capacities for testosterone production.

Methods

A dose of 0.2 mg TRH (Relefact: Hoechst) was given i.v. during 30 sec to 8 infertile men with non-obstructive azoospermia and low testosterone levels (Groups 1 and 2) and to 7 normospermic males (Group 3) who acted as controls. None of the men investigated had received any medication for at least 12 weeks before the experiment. Groups 1 and 2 each contained 4 men with Klinefelter's syndrome and 4 men with Sertoli cell-only syndrome, both conditions being confirmed karyotypically and by testicular biopsy. Blood samples were withdrawn through a Venflow intravenous cannula before and 15, 30, 60, 120 and 180 min after the TRH injection. The experiments were performed be-

tween 11.00 and 14.00 h. Blood samples were incubated overnight at 37°C, centrifuged at 1200 g, and the sera kept at -21°C until assayed.

Prolactin levels were measured by the NIAMDD radioimmunoassay kit VLS-2, as instructed, except for minor modifications. All samples were run in two dilutions in triplicate, and the mean for each assay was used for the statistical calculations. The sensitivity of the prolactin assay was approximately 0.2 ng, and prolactin values are expressed in terms of h-PRL-VLS-2. The results were analysed using the Student's *t* test.

Table 1. Serum prolactin levels (ng/100 ml) in infertile males with Klinefelter's syndrome (Group 1) and Sertoli cell-only syndrome (Group 2) and low testosterone values, and in fertile normospermic males with normal testosterone levels (Group 3) in their response to TRH

	Time after TRH (min)						Testosterone (ng/100 ml)
	0	15	30	60	120	180	
Group 1							
PM	22.1	29.0	24.0	20.1	12.1	20.2	100
LI	19.0	28.0	19.0	21.2	15.2	11.0	137
RE	16.1	25.0	25.0	22.0	18.4	20.3	145
GA	22.4	20.9	18.0	24.8	18.9	16.6	98
Mean $\pm$ S.E.M.	19.9 $\pm$ 1.5	25.7 $\pm$ 1.8*	21.5 $\pm$ 1.8	22.0 $\pm$ 1.0	16.2 $\pm$ 1.6	17.0 $\pm$ 2.2	120 $\pm$ 12
Group 2							
ON	24.2	23.0	23.8	23.9	22.0	22.0	101
MF	16.4	21.0	21.0	14.1	14.1	17.1	134
LP	17.0	25.0	21.0	23.4	14.5	15.0	120
AS	15.5	23.0	23.0	15.0	18.0	15.0	150
Mean $\pm$ S.E.M.	18.3 $\pm$ 2.0	23.0 $\pm$ 0.8*	22.2 $\pm$ 0.7*	19.1 $\pm$ 2.6	17.2 $\pm$ 1.8	17.3 $\pm$ 1.7	126 $\pm$ 10
Group 3							
BN	19.1	44.1	27.2	24.5	23.0	23.3	600
SD	19.4	44.3	27.0	24.4	23.4	23.0	350
AR	17.2	34.0	27.0	17.3	18.4	16.1	500
RM	12.1	31.0	25.0	21.0	15.1	21.5	450
SA	12.3	26.1	20.1	17.2	10.1	11.2	320
CE	19.0	43.8	26.2	24.1	23.0	23.1	250
MB	12.3	30.0	24.2	21.3	15.2	21.4	300
Mean $\pm$ S.E.M.	15.9 $\pm$ 1.3	36.2 $\pm$ 2.9*	25.2 $\pm$ 0.9*	21.4 $\pm$ 1.2*	18.3 $\pm$ 1.9	19.9 $\pm$ 1.7	395 $\pm$ 47

* Significant elevation as compared to the value at 0 time; *P* < 0.05.

Results and discussion

The men in all three groups had similar basal values of serum prolactin, but the response to TRH varied (Table 1). In Groups 1 and 2 serum prolactin levels after TRH injection were increased by 29 and 26% at 15 min but basal again by 30 and 60 min respectively. In the control men (Group 3), serum prolactin levels increased rapidly to a peak of 127% above the basal value by 15 min and the pretreatment levels were reached by 2 h after injection. Two additional azoospermic males, one with Klinefelter's syndrome and one with Sertoli cell-only syndrome, had normal testosterone values (therefore not included in the table) and responded to TRH administration as did the control, normospermic males with increases of 126% and 150% above basal levels within 15 min, suggesting that the testosterone level may have a priming function in this hormonal response.

Normal prolactin values in patients with Klinefelter's syndrome were reported by Aubert *et al.* (1973). Burman *et al.* (1975) claim that such patients over-respond to TRH at 15 min after i.v. administration, but most of their patients exhibited normal testosterone levels (473 ± 53 ng/100 ml; range 238–477 ng/100 ml). Our patients which were homogeneous as far as pretreatment levels of testosterone were concerned nearly all responded to TRH, but the response was greater when testosterone levels were higher.

Our findings are in accord with those recently obtained by Cheikh, Hamilton, Hsu & Wiswell (1975), who found normal basal plasma prolactin concentrations in four patients with Klinefelter's syndrome, with abnormal elevation during testosterone administration. In view of these results, the correlation between the three factors of sperm count, testosterone levels and pituitary response to TRH administration warrants further investigation.

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