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II. The TRH Test

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Summary: Anterior pituitary response to TRH 200 μg i.v. was studied in ten chronic schizophrenic patients during long-term neuroleptic treatment. Nine patients had normal prolactin (PRL) response as compared with controls but in one the response was blunted; one patient had an exaggerated response. Prolactin increment was higher following TRH than haloperidol challenge. No growth hormone (GH) response to TRH was found and TSH responses were comparable to controls.

Although the acute effects of neuroleptic drugs in increasing prolactin (PRL) secretion by the anterior pituitary are well documented (e.g. Gruen *et al*, 1978), less is known of the effects of long-term neuroleptic treatment. Plasma PRL levels within the normal range have been described in schizophrenic patients on

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chronic neuroleptic medication (Naber *et al*, 1979; Beumont *et al*, 1974). Failure of an increase in neuroleptic dose to elicit a further PRL release is reported by several authors (see part 1 of this series of studies). Inability of the pituitary to increase PRL secretion as a consequence of chronic stimulation by dopamine (DA) blockade, might underlie these observations.

Neuroendocrine tests with DA antagonists and agonists, as described in other parts of this series of studies, were carried out to assess the degree of DA receptor blockade produced by the patients' current medication (see the preceding and following companion papers; also Kolakowska *et al*, 1981). In the study described here, the TRH test was carried out during neuroleptic treatment to complement the previously described haloperidol test (whose results were not known at the time), to compare plasma PRL responses to TRH and to haloperidol, and to explore the usefulness of the TRH test as an index of pituitary ability to secrete prolactin in cases where no PRL response to haloperidol occurred.

Thyrotropin releasing hormone (TRH) acts directly on the pituitary (Diefenbach *et al*, 1976) and stimulates a dose dependent plasma PRL rise; TRH 200 mg i.v. elicits a maximal PRL response (Jacobs *et al*, 1971; Bowers *et al*, 1971). Single doses of oral neuroleptics produced conflicting effects on the TRH-induced PRL rise in normals (Linnoila *et al*, 1978); the effects of acute parenteral administration have not been studied. Naber *et al* (1979) found PRL responses to TRH 200 mg i.v. comparable to normals, in schizophrenic patients on chronic neuroleptic treatment. Challenge with TRH was used in the study described below, to compare pituitary hormone responses in schizophrenic patients on chronic neuroleptic treatment with unmedicated controls.

Subjects and Method

Eight male patients (for details see preceding communication, Table I, nos. 3, 13, 14, 16–20) and two female patients (no. 21—on depot fluphenazine decanoate 6.25 mg/week, total duration of treatment 10+ years; no. 22—on flupenthixol decanoate 40 mg/week, total duration of treatment 4.5 years) underwent a haloperidol test (test 1) as described previously. On a separate occasion, at least one week later, all but female patient no. 22 underwent a second test where TRH 200 μg i.v. was given in lieu of haloperidol, the procedure being otherwise the same, with the withdrawal of an additional blood sample at fifteen minutes (TRH test).

Six normal men (mean age 31.8 ± 4.6 years) and one normal woman (age 29 years) also underwent TRH tests as described above.

Female patient no. 22, while receiving oral flupenthixol 12 mg/day in addition to her (above) depot medication, underwent a second haloperidol test. On this occasion, TRH 200 μg i.v. was given 150 minutes after 4 mg haloperidol i.m., and 4 further blood samples were collected over 60 minutes (test 2).

The hormones measured were plasma prolactin (radio-immunoassay, as described previously), growth hormone (radio-immunoassay kit, Sorin Biomedica) and serum thyroid stimulating hormone (radio-immunoassay, Hall *et al*, 1971; R. F. Smith, unpublished modification).

TABLE I

Plasma prolactin during TRH and haloperidol tests in 9 subjects

	Subjects		Plasma prolactin (Miu/L)		
			TRH test		Haloperidol test
No.	Sex	Age	Baseline	△PRL	△PRL
3	M	67	510	1860	1086
13	M	54	530	780	440
14	M	56	368	912	1290
17	M	55	386	1094	456
19	M	42	436	464	420
20	M	32	546	2034	1272
16	M	58	1950	420	180
18	M	60	2550	1470	800
21	F	44	554	1776	1220
Mean △PRL ± SD				1201 ± 607*	796 ± 433

* △PRL TRH test > △PRL haloperidol test; t = 3.15; P < 0.02 (two-tailed paired t-test).

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Results

Plasma PRL level at 0 minutes (baseline) was within the normal range for males in this laboratory (under 616 miu/L) in 6 of the 8 male patients (all but nos. 16 and 18, Table I). Prolactin response to TRH of these subjects was similar to that of the 6 male controls (Fig 1a). Although mean baseline PRL level was higher in the 6 'normal baseline' patients than in controls (Mean ± SD: 462 ± 76 miu/L and 277 ± 101 miu/L respectively, P <0.02), the maximum PRL increment (△PRL) did not differ between the groups (Mean ± SD: 1190 ± 623 miu/L and 870 ± 355 miu/L, difference not significant).

Of the 2 male patients with elevated baseline PRL (Fig 1b), one showed a PRL response comparable to the 'normal baseline' patient group (no. 18; △PRL 1470), while in the other △PRL was much smaller (no. 16; 420 miu/L). Female patient (no. 21) whose baseline PRL at 594 miu/L was within the normal range for females for this laboratory (100–638 miu/L), responded to TRH with a large PRL rise (△PRL 1776 miu/L) comparable to what has been found for normal females (Jacobs *et al*, 1973). The second female patient (no. 22) had a high baseline PRL in both test 1 and test 2 (4400 miu/L; 3050 miu/L respectively). Peak PRL level after haloperidol was the same for both tests (6700 miu/L; 6600 miu/L) and a similar maximum level was found after TRH in test 2 (PRL at 150 mins. before TRH—5000 miu/L; post-TRH—7100 miu/L).

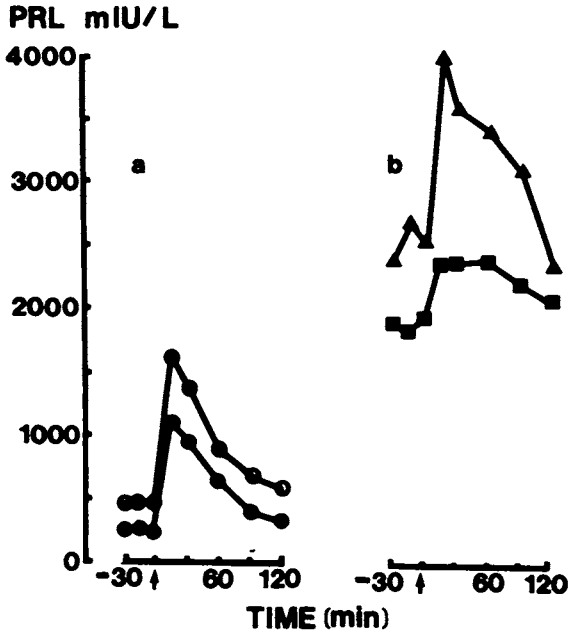


FIG 1.—Plasma prolactin (PRL) response to TRH 200 μg i.v. TRH administration at '0' time indicated by an arrow.
(a) Mean plasma PRL of 6 male control subjects (●——●) and 6 normal baseline patients (○——○).
(b) Plasma PRL levels of 2 male patients with elevated PRL baseline (No. 16 ■——■; No. 18 ▲——▲).

Prolactin responses to TRH and to haloperidol in 9 patients who were tested separately with each challenge, are compared in Table I. Prolactin peak occurred at 15 minutes after TRH, but later and more variably (30–150 minutes) after haloperidol. Prolactin increment was higher after TRH than following haloperidol in 8 of the 9 patients (all but no. 14) and the difference was significant at P <0.02.

In patient no. 16 who showed little if any PRL response to haloperidol (△PRL 180 miu/L, baseline PRL 2070 miu/L), TRH elicited a prolactin rise (△PRL 420 miu/L, baseline 1950 miu/L).

There were no changes in GH following TRH in either patients or controls, with the exception of patient no. 22 who showed marked GH elevations after haloperidol (GH = 8.4 ng/ml) and after TRH (GH = 20.3 ng/ml). Mean baseline TSH levels and peak TSH responses to TRH for patients were not significantly different from controls.

Discussion

Prolactin response to TRH in patients with 'normal PRL baseline' was comparable to that of controls. This is in agreement with previous findings (Naber *et al*, 1979) and suggests that a PRL level within normal limits in chronically treated patients is not due to inability of the pituitary to secrete more prolactin. Prolactin responses to TRH in 2 patients with high baseline levels (nos. 18 and 22) were comparable to those of 'normal baseline' patients, suggesting that PRL response to TRH is preserved during chronic neuroleptic treatment across a wide range of baseline secretion.

The earlier PRL peak (at 15 minutes) after TRH compared to haloperidol (30–150 minutes) is probably related to the mode of administration (i.v. and i.m. respectively). However, peak plasma haloperidol levels were found to precede peak PRL levels by 30–60 minutes, as described in the previous communication. This suggests that the discrepancy may also be related to the different mode of action at the pituitary of the two drugs.

Comparison of data from TRH and haloperidol tests is of particular interest in patients nos. 22 and 16. The similar peak PRL levels in the 2 haloperidol tests and following TRH in patient no. 22 suggest that in this case a maximum prolactin response was reached. This may represent the maximal response of the pituitary to a stimulus inducing prolactin release, or be

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due to negative feedback operating to maintain plasma prolactin below a certain level. In patient no. 16 who was on high doses of neuroleptics (prochlorperazine 45 mg/day), a negligible PRL rise following haloperidol and a small although definite response to TRH suggest that the high baseline PRL in this patient represented a near maximum PRL secretion by the pituitary. Patient no. 16 had had a leucotomy however, and while it is not clear how this would affect pituitary function, these results should be viewed with caution.

The growth hormone elevations in patient no. 22 following both haloperidol and TRH suggest a non-specific stress response, as growth hormone levels should fall after dopamine blockade by haloperidol.

In conclusion, in this study of ten schizophrenic patients on chronic neuroleptic treatment, all but one showed prolactin responses to TRH comparable to those of normal controls. No growth hormone responses were found and TSH responses were comparable to controls. The TRH test was able to demonstrate the pituitary's ability to release prolactin in one patient who did not show a marked PRL rise after haloperidol challenge. This might have further application in cases where the haloperidol test is negative.

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