

Acta Medica Okayama

Volume 34, Issue 4

1980

Article 5

SEPTEMBER 1980

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Abstract

The effects of oral and intravenous thyrotropin-releasing hormone (TRH) were studied in 11 male, chronic schizophrenic inpatients in an open trial and a double-blind, crossover design. The general beneficial effects of TRH as assessed on the Brief Psychiatric Rating Scale were not obtained, although improvement of contact, apathy and emotional rapport was observed in a few patients. Serum prolactin, L-triiodothyronine and thyroxine were assayed throughout the study. Since the effects of TRH on behavior were not related to changes in these endocrine factors, the mechanism of action might be independent of its original functions on the pituitary-thyroid axis.

KEYWORDS: thyrotropin-releasing hormone, prolactin, L-triiodothyronine, thyroxine, schizophrenia

*PMID: 6452029 [PubMed - indexed for MEDLINE]

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Acta Med. Okayama **34**, (4), 263—273 (1980)

EFFECTS OF THYROTROPIN-RELEASING HORMONE IN CHRONIC SCHIZOPHRENIC PATIENTS

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Received May 1, 1980

Abstract. The effects of oral and intravenous thyrotropin-releasing hormone (TRH) were studied in 11 male, chronic schizophrenic inpatients in an open trial and a double-blind, crossover design. The general beneficial effects of TRH as assessed on the Brief Psychiatric Rating Scale were not obtained, although improvement of contact, apathy and emotional rapport was observed in a few patients. Serum prolactin, L-triiodothyronine and thyroxine were assayed throughout the study. Since the effects of TRH on behavior were not related to changes in these endocrine factors, the mechanism of action might be independent of its original functions on the pituitary-thyroid axis.

Key words: thyrotropin-releasing hormone, prolactin,
L-triiodothyronine, thyroxine, schizophrenia

Thyrotropin-releasing hormone (TRH), one of the hypothalamic hypophyseotropic hormones, is widely distributed in animal (1, 2) and human brains (3), and exerts a great variety of behavioral effects in animals (4). Recent investigations have suggested that this hormone might play a role in brain function independent of its effects on the pituitary-thyroid axis (4). In man, Prange *et al.* (5) first reported that TRH caused a rapid but brief, partially beneficial effect in a double-blind, crossover study of 10 women with unipolar depression. These workers then treated 10 normal women with TRH and found that the subjects experienced relaxation, mild euphoria and a sense of increased energy (6). In 1973, Wilson *et al.* (7) reported that TRH exerted rapid overall beneficial effects in schizophrenia, *i.e.*, emotional warmth, lucidity of thought and accessibility to psychotherapy, within a few hours of injection. However, there are conflicting reports on the behavioral effects of TRH in schizophrenia as mentioned later.

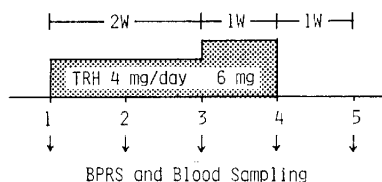
In the present investigation, we studied the effects of oral and intravenous TRH in 11 chronic schizophrenic patients. In order to determine whether the

behavioral effects of TRH are related to changes in pituitary-thyroid function, serum prolactin (PRL), L-triiodothyronine (T_3) and thyroxine (T_4) were assayed throughout the study. Platelet monoamine oxidase (MAO) activity was also estimated to examine changes due to altered thyroid function during TRH treatment.

MATERIALS AND METHODS

Eleven male, chronic schizophrenic inpatients with a family history of schizophrenia, aged 19 to 58 years, participated in this study. The diagnosis was made according to the criteria of Feighner *et al.* (8) and Kolb (9). Informed consent was obtained from patients. The present study consists of two series performed in August and December 1979, as shown in Fig. 1. In the first series, the patients

1) The First Series (Oral Administration)



2) The Second Series (Intravenous Administration)

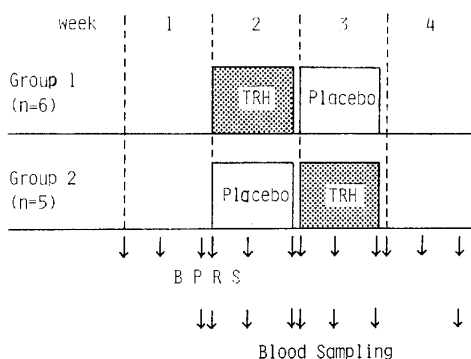


Fig. 1. Schedules of TRH treatment

received oral TRH tartrate, 4 mg per day for 2 weeks and 6 mg for an additional week, in an open trial. Previous neuroleptic medications remained unchanged. To evaluate behavioral changes, the patients were assessed on the Brief Psychiatric Rating Scale (BPRS) (10) before TRH administration, then weekly during the following 4 weeks. BPRS consists of 16 items, each of which is scored from 1 (no symptoms) to 7 (severe symptoms). On the same day at 10 a.m. (two hours after the morning medication), 15 ml of venous blood was withdrawn from each patient for biochemical measurements. Platelet and serum were isolated by standard procedures, and kept in a freezer at -20°C until assay. Serum levels of PRL, T_3

and T_4 were determined by radioimmunoassay using CIS kit for PRL and PEG Riapac for T_3 and T_4 . Platelet MAO activity was determined by a radioisotopic method using tryptamine as substrate, as described elsewhere (11).

The second series was a double-blind, placebo-controlled, crossover study with intravenous TRH tartrate. Eleven patients were randomly divided into two groups according to a prearranged schedule. After baseline assessment for a week, six patients (group 1) were injected intravenously with TRH (0.5 mg in 5 ml of 20% glucose) at 9 a.m. daily in the first week, and then with a placebo (5 ml of 20% glucose) in the second week. Five patients (group 2) were treated in the identical manner, except that the placebo was injected in the first week and TRH in the second week. At regular intervals, three times weekly, the patients were assessed on the BPRS and blood was withdrawn at 10 a.m. (one hour after TRH or placebo injection) in the days shown in Fig. 1.

Student's t-test was used to test statistical differences.

RESULTS

Behavioral Findings

Fig. 2 shows behavioral changes in the first series as represented by BPRS

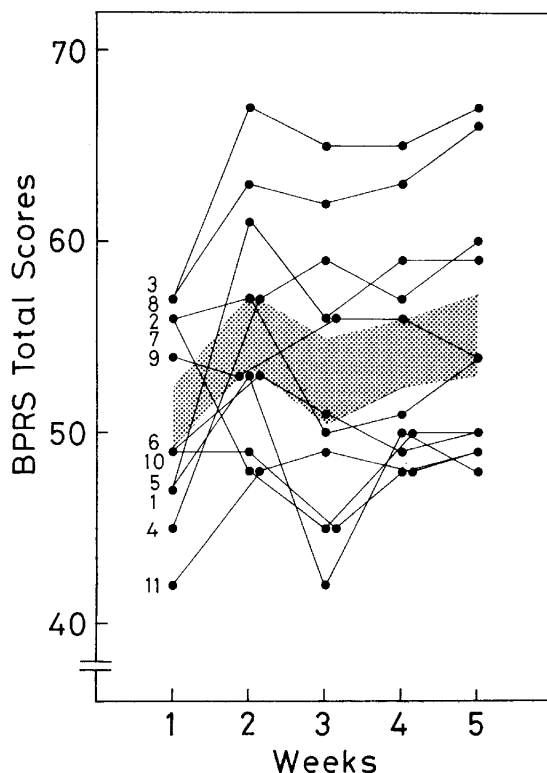


Fig. 2. BPRS total scores at baseline (week 1) and after oral TRH administration. Small numerals indicate the case number. Mean values \pm S.E.M. are shown as shaded areas.

total scores. The total scores in week 2 increased in 8 of 11 patients. The mean scores shown as shaded areas in Fig. 1 tended to be higher during and after TRH treatment than the baseline, but this failed to reach statistical significance. Among items on BPRS, the scores of somatic concern and mannerisms-posturing increased significantly during the third week of treatment (week 4) compared with the baseline period, and the former was still high one week after cessation of TRH (week 5). Anxiety and tension were also significantly higher in week 5 than in week 1. Guilt feelings increased in weeks 2 and 5. On the other hand, emotional withdrawal tended to decrease in weeks 3 and 4, but this decrease failed to reach statistical significance. Independent of changes in BPRS scores, improvement was observed in apathy and emotional rapport in case 1, contact in cases 2 and 9, and negativism in case 7.

Fig. 3 represents behavioral changes in the crossover study with intravenous

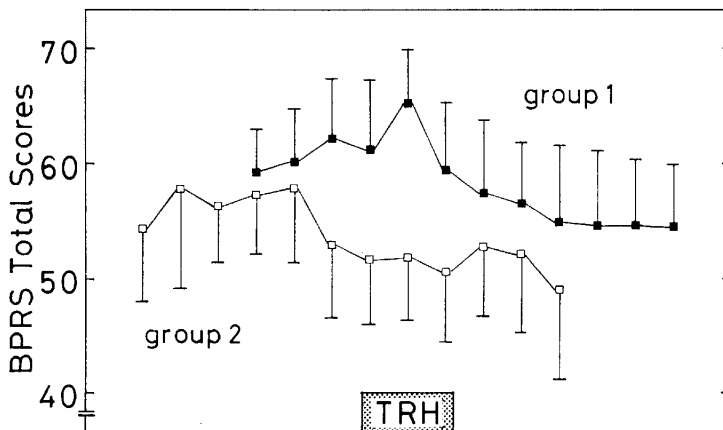


Fig. 3. BPRS total scores of two treatment groups at baseline and after injections. Points during TRH treatment in two groups are overlapped in the figure. Vertical bars indicate \pm S.D.

TRH. In group 1 patients treated with initial TRH followed by placebo, the total scores appeared to decrease after TRH administration. While a similar tendency was found in group 2, decreased scores were evident during placebo administration preceding TRH. Among items on BPRS, TRH produced an improvement in guilt feeling and depressed mood during and after treatment in both groups. The patients showed an improvement of contact in cases 1 and 2, decreased mental viscosity in case 6, and reduced apathy with slightly elevated psychomotor activity in case 7. During the intravenous TRH treatment one patient complained of mild nausea. No other side-effects were found.

Biochemical Findings

Serum prolactin (PRL). Serum PRL levels during oral TRH treatment increased slightly, but not significantly, compared with the baseline levels. Intravenous TRH significantly increased PRL levels in the second series as shown in Fig. 4. However, no correlation was found between behavioral changes and PRL responses either as a whole or in each case. As shown in Table 1, the

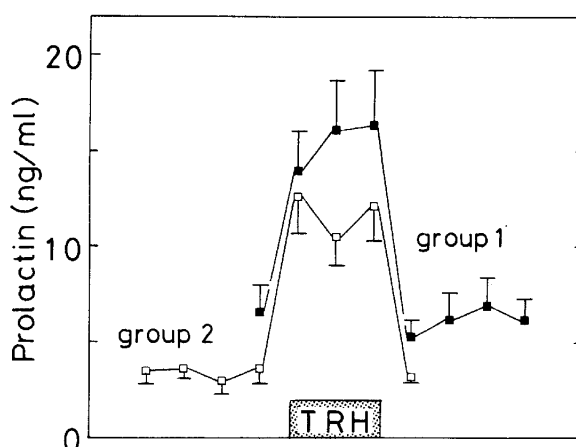


Fig. 4. Serum PRL levels of two treatment groups at baseline and after injections. Points during TRH treatment in two groups are overlapped in the figure. Vertical bars indicate \pm S. E. M.

Table 1. SERUM PROLACTIN LEVELS (ng/ml)

Controls (n=28)	9.64 \pm 0.86
Schizophrenics (n=11)	
1st series	9.53 \pm 1.79
2nd series	5.21 \pm 0.92*

Values are means \pm S. E. M. for the number of cases in brackets.

* Significantly different ($p < 0.01$) from controls.

mean baseline values for the schizophrenic patients in the first series were not different from our control values for 28 normal men, although the patients received long-term neuroleptic treatment. In the 2nd series, on the other hand, the baseline values were significantly lower than the control. The reason for the difference in the two baseline values for the same patients is not clear.

Serum L-triiodothyronine (T_3). Serum T_3 levels were higher, but not significant, during oral TRH treatment than the baseline. On intravenous administration of TRH, the patients in both groups showed no significant changes in T_3

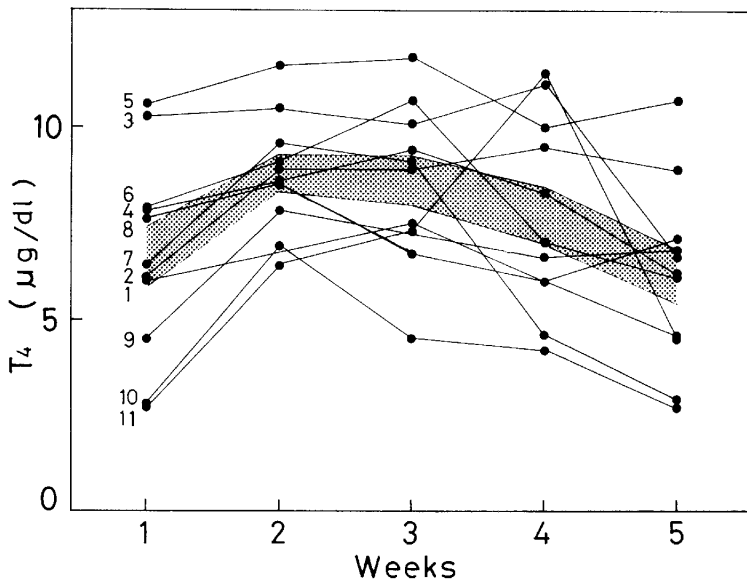


Fig. 5. Serum T₄ levels at baseline and after oral TRH administrations. Mean values \pm S. E. M. are shown as shaded areas.

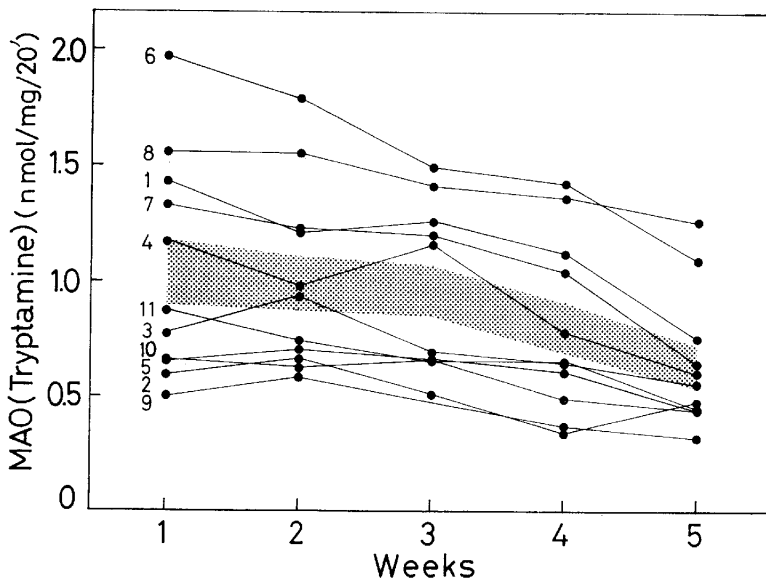


Fig. 6. Platelet MAO activities using tryptamine as substrate at baseline and after oral TRH administrations. Small numerals indicate the case number. Mean values \pm S. E. M. are shown as shaded areas.

values. No correlation was found between behavioral changes and T_3 responses.

Serum thyroxine (T_4). One week after oral TRH administration (week 2) serum T_4 levels increased in all patients and the mean values were significantly higher than the baseline (Fig. 5). However, such changes in T_4 values did not correlate with behavioral changes. In the second series with intravenous TRH there were no significant changes in serum T_4 .

Platelet monoamine oxidase (MAO). Fig. 6 shows changes in MAO activity due to oral TRH administration. The mean MAO activity was significantly reduced in weeks 4 and 5 compared with week 1. However, the reduced MAO activity did not correlate with changes in serum T_3 or T_4 values. No significant changes in MAO activity were found by intravenous TRH administration.

DISCUSSION

Inanaga *et al.* (12) obtained a favorable response in about 74% of 62 chronic schizophrenic patients treated with orally administered TRH, who showed prominently reduced spontaneity, abulia, apathy and social withdrawal. They then performed a double-blind, controlled study of 143 similar patients with oral TRH (4 mg per day for 14 days), and reported that TRH appeared to be significantly superior to the placebo in regard to the patients' symptoms such as motivation for work, facial expression, emotional rapport and psychomotor activity (13). Recently, Prange *et al.* (14) treated 12 schizophrenic patients with a single intravenous injection of 0.5 mg TRH under double-blind conditions. The patients showed about a 50% prompt decrease in psychotic symptoms, most prominently in thinking disorder. This effect persisted for at least two weeks with gradual relapse. There are 4 other studies reporting favorable effects of TRH in autistic schizophrenic children (15) and schizophrenic patients (7, 16, 17).

On the other hand, Drayson (18) reported the ineffectiveness of intravenous TRH in cyclical psychoses. The lack of behavioral changes was also reported by Clark *et al.* (19) in a double-blind, crossover study with oral TRH (300 mg per day over three weeks) in 12 schizophrenic patients, and by Lindström *et al.* (20) in a double-blind, crossover study with intravenous TRH (0.6 mg for 4 consecutive days) in 10 drug-free schizophrenic patients. Bigelow *et al.* (21) found slight worsening of depression in 2 of 3 drug-free schizophrenic patients after intravenous TRH (0.6 mg) for 5 days. In the study of Davis *et al.* (22) using 300 mg per day of oral TRH, seven of 9 patients showed worsening of symptoms, especially in the patients with paranoid schizophrenia. Thus, the results are conflicting with respect to the effects of TRH in schizophrenia.

In the present investigation we found no overall beneficial effects of TRH in 11 chronic schizophrenic patients with either oral or intravenous administra-

tion. In the first series with oral TRH, the treatment appeared to aggravate symptoms such as somatic concern, mannerisms and posturing, anxiety, tension, and guilt feelings. The only improved symptom was emotional withdrawal. There was nothing conclusive in the second series with intravenous TRH, although depressed mood and guilt feelings appeared to be improved. However, it should be kept in mind that, independent of changes in BPRS scores, a few patients showed improvement of contact, apathy and emotional rapport. One of the reasons for above-mentioned conflicting results might be differences in the population of the subjects in each study. While Inanaga and his colleagues obtained good results in selected patients with loss of spontaneity, apathy, abulia, and contact disturbances, the patients were not selected in regard to symptoms in other studies including ours. Numeroff *et al.* (4) stated that "chronic schizophrenic patients tend to benefit from TRH if they are not paranoid and especially if they prominently display symptoms of social withdrawal, abulia and adhedonia".

The mechanism of action of TRH in schizophrenia is unknown. While the most plausible mechanism is that TRH acts via the pituitary-thyroid axis, Inanaga *et al.* (13) found no changes in T_4 dynamics in oral TRH-treated patients. With intravenously administered TRH, on the other hand, Prange *et al.* (14) reported that the patients showed lower T_3 values at baseline, brisker T_3 response after injection and elevated free T_4 at baseline and 90 min after injection compared with controls. However, these endocrine findings were not related to behavioral changes. In the present study, there was no relationship between behavioral changes and changes in the levels of serum PRL, T_3 and T_4 . Thus one can not relate the behavioral effects of TRH to hypophyseal or thyroidal changes. It has been noted in animal experiments that TRH potentiated the stimulant effects of Dopa plus pargyline (23) and the behavioral effects of increased 5-hydroxytryptamine accumulation (24). However, these investigators pointed out that the phenomenon was independent of a TSH-mediated effect on thyroid function, since the potentiation occurred even in hypophysectomized animals.

On the other hand, Keller *et al.* (25) reported that TRH enhanced the turnover of noradrenaline in the intact and thyroidectomized rat brain. This evidence has been confirmed by Horst *et al.* (26) and Marek *et al.* (27). Clinically interesting is the observation of Inanaga and his colleagues that schizophrenic patients responding to small doses of L-Dopa also responded to TRH treatment (16, 17, 28). They suggest that the mechanism of action common to L-Dopa and TRH exerts a favorable effect on some kinds of schizophrenic symptoms. At present, however, there is little reliable information available on the central or direct action of TRH. Further studies are necessary to clarify the mechanism

of action.

It is well known that various neuroleptics raise serum PRL levels through disinhibition of PRL secretion by binding to and blocking dopamine receptors (29). While several investigators have reported that tolerance did not develop in the PRL response to neuroleptics (30, 31), we obtained opposite results indicating acquired tolerance after long-term levomepromazine (32) and chlorpromazine treatment (unpublished data). The fact that the PRL levels in 11 schizophrenic patients on long-term neuroleptics were not higher than those of normal controls in this study may support this concept.

Since Murphy and Wyatt's report (33) of lower platelet MAO activity in chronic schizophrenic patients than in normal controls, numerous follow-up studies have appeared in the literature. Some investigators confirmed this finding, but others did not (34). Of the many factors known to affect MAO activity, thyroid hormones have been reported to influence MAO in other organs such as heart, liver, kidney and salivary glands (35-37). Although, in this study, platelet MAO activity was reduced by oral TRH administration, the reduction in activity did not correlate with changes in serum T_3 or T_4 values. Murphy *et al.* also reported no correlation between serum T_3 and platelet MAO activity (33).

Acknowledgments. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture (No. 237037). TRH tartrate was kindly furnished by Takeda Chemical Industries Ltd. We are grateful to Miss Sanae Kageyama and Miss Eiko Nishioka for skilfull technical assistance and to Miss Akiko Takizawa for preparing the manuscript.

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