EFFECTS OF THYROTROPIN-RELEASING HORMONE IN DEPRESSION*

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Summary Ten euthyroid women with unipolar depression were treated with a single injection of thyrotropin-releasing hormone (T.R.H.) and a single injection of saline in a double-blind, cross-over comparison. T.R.H. caused a prompt, brief improvement in depression without causing significant side-effects Most patients showed a reduced thyrotropin (T.S.H.) response to T.R.H. injection, though none had abnormal thyroid function tests or clinical findings suggesting pituitary or thyroid disease.

Introduction

THYROTROPIN-RELEASING hormone (T.R.H.), a substance of hypothalamic origin, is a potent and non-toxic stimulator of pituitary thyrotropin (T.S.H.) [1,2] and pituitary prolactin [3,4] in man. Our interest in T.R.H. (or any agent that would cause T.S.H. release) stems from our work demonstrating that L-triiodothyronine (T3) will potentiate the antidepressant effects of tricyclic drugs in women.[5–11] Further work by our group indicated that T.S.H. also potentiates tricyclic antidepressants, presumably by causing release of thyroid hormones.[12,13]

These findings prompted us to examine the psychopharmacological effects of T.R.H. in animals. With N. P. Plotnikoff, we investigated the activity of T.R.H. in the pargyline/L-dopa potentiation test, which has been used to screen drugs for antidepressant potential.[14] T.R.H. was active in this test and, surprisingly, was equally active in intact and hypophysectomised mice.[15] These data suggest that L-dopa potentiation by T.R.H. in animals is not mediated via increased secretion of T.S.H. or thyroid hormones and that an extra-pituitary mechanism is at work. Although this study did not clarify the mechanisms for our earlier findings,

it did suggest that T.R.H. might have antidepressant activity. We present here our observations on eighteen depressed women who were treated with intravenous T.R.H.

To discern proper dose and possible toxicity, we studied eight women with unipolar depression in a flexible single-blind study. A single intravenous injection of T.R.H., from 200 to 800 μg., seemed sufficient to cause prompt, brief, clinical improvement. 500–600 μg. seemed more effective than smaller doses. One woman received 800 μg. Although generally improved she complained that she felt "jittery" for a few hours. Several patients experienced a sensation of slight warmth shortly after injection. It seemed possible largely to avoid this effect by using a full minute to inject the hormone. No other side-effects were noted, and there was no evidence of toxicity due to T.R.H. Other data pertaining to these eight patients have been excluded from the present report.

Patients and Methods

A double-blind cross-over study against placebo injection was designed. Women between the ages of 25 and 45 admitted to the Dorothea Dix Hospital with primary [16] unipolar [17] depression were admitted to the study and transferred to the research unit if they gave informed consent, if they did not use oral contraceptive preparations, if they presented no physical, historical, or chemical evidence of thyroid disorder, and if they were generally in good physical health and were not pregnant. Most patients had taken small amounts of various psychotropic drugs for brief periods of time. We stopped these medications and then gave thrice daily two capsules of placebo which matched imipramine. If, after 7–10 days of placebo medication and general care, the patient still scored substantially on the Hamilton rating scale for depression (H.R.S.) (18), the patient was assigned to group A (five patients) or group B (five patients) according to a prearranged schedule balanced for age. We did not distinguish between the various possible descriptive subtypes of unipolar depression because such distinctions have not been useful in our previous studies.

Group A patients were treated as follows. After baseline assessments, the patient lay supine in bed. A continuous intravenous infusion was begun in one arm; a blood-pressure cuff was attached to the other arm. At 9 A.M., 2 hours after breakfast, 600 μg. T.R.H. was slowly injected into the intravenous tubing. At regular intervals blood was withdrawn for later analyses of T.S.H. by specific radioimmunoassay,[19] thyroxine (T4) iodine,[20] residual T4 binding space,[21] and total serum-T3,[22] baseline samples having been obtained earlier. The nurse giving the injections was in sole possession of the medication code. Apart from the injections she had no immediate responsibility to this group of patients. Another nurse, obtaining blood-pressure and pulse recordings regularly, sat with the patient and conversed or remained silent, according to the patient's wish. The patient was allowed out of bed at noon.

A psychiatrist visited the patient at 8 A.M. and hourly thereafter until 3 P.M., except at 1 P.M. At 3 P.M. he did an H.R.S. assessment and the patient completed the Taylor manifest anxiety scale (T.A.S.).[23] At each hourly session the psychiatrist asked the patient to perform the 100 mm. line test. (In this test a 100 mm. line is drawn on a sheet of plain paper and one end is identified "As well as I could be", the other end "As depressed as I could be". The patient marks where she stands at the moment of testing. The score, the length in millimetres from the "well" end of the line, is based on the premise that length is analogous to the severity of the depression.[24,25]) After each hourly session he immediately dictated the results of a brief, informal mental-status examination and inventory of side-effects. At the end of the study another psychiatrist "blindly" assigned numerical values to transcriptions of the mental-status examinations. His ratings were intended to be analogous to scores from the H.R.S.

Ankle-reflex time [26] was measured at 3 P.M. on injection days and throughout the study.

A week after the T.R.H. injection, group-A patients repeated the same procedure, except that saline solution was infused in place of T.R.H. The same nurse attended, and blood was taken again regularly, though not all of it was assayed for T.S.H.

Group-B patients were treated in an identical manner, except that saline was injected the first week and T.R.H. the second. No other medication than T.R.H. was used during the project. Only one injection of T.R.H. was given to each patient because we were then uncertain of the safety of repeated doses. Placebo capsules were given throughout.

Results

Although our number of patients was small, equal cell size and placebo cross-over provided considerable statistical power. We subjected the data to analysis of variance according to Winer's technique for repeated measurements [27] to examine the baseline inequalities between groups (none was significant), interaction, and order effects. By far the greatest differences were caused by treatments—i.e., by the differential use of T.R.H. and saline solution. To test these differences we employed Seal's multivariate technique using orthogonal vectors.[28] Data from group A (first injection, T.R.H.) were combined with data from group B (second injection, T.R.H.). These data were then compared with the data from the two groups when saline was administered.

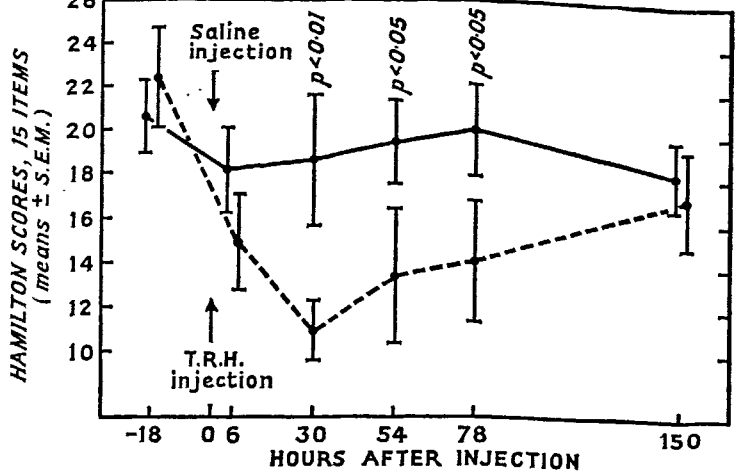
Three different periods after injection were examined according to two objectives and two subjective measures of change. To examine for H.R.S. and T.A.S. changes we used the 3 P.M. scores from the pre-injection days as baselines (table I). T.R.H. was superior to saline in five of twelve instances. Saline was never superior to T.R.H.

While examining table I, one should recall that on injection days the 100 mm. line test and the mental-status examination were performed seven times (two baseline plus five), while the H.R.S. and the T.A.S. were performed only once. Thus there was agreement between the objective and subjective scales performed frequently and agreement between the objective and subjective scales performed infrequently.

TABLE I—ADVANTAGES OF T.R.H. INJECTION ON VARIOUS MEASURES OF MENTAL STATE FOR VARIOUS PERIODS AFTER INJECTION

Test	Assessor	Injection day (P)	Injection day + 1 (P)	Injection day + 1, 2, 3 (P)
100 mm. line	Patient	< 0·01	N.S.	N.S.
Mental-status examination ..	Psychiatrist	< 0·01	N.S.	N.S.
Taylor manifest anxiety scale ..	Patient	N.S.	N.S.	< 0·01
Hamilton rating scale	Psychiatrist	N.S.	< 0·01	< 0·01

N.S. = Not significant.



Changes in Hamilton rating scale scores caused by a single injection of T.R.H. or saline solution.

On the day of T.R.H. injection patients tended to be unchanged for an hour, to improve strikingly late in the morning, and then to relapse toward baseline toward mid-afternoon. After saline solution, patients tended to express somatic complaints, often related to enforced immobility in bed. After arising at noon they improved somewhat, this being determined probably in part by diurnal variation in the depression process.

Although the beneficial effects of T.R.H. seemed by some measures to dissipate quickly, according to other measures they persisted. The figure shows the results of the H.R.S. over the course of the study. An H.R.S. item analysis indicated that psychic symptoms improved more than somatic ones.

Despite slow injection two patients reported a mild sensation of warmth within 30 minutes of the T.R.H. injection, one after saline injection. Obviously this side-effect was too unreliable to have identified the medication used. No other side-effects and no evidence of toxicity were found.

The physiological and chemical findings seem as important as the clinical ones. Table II shows that after the injection of T.R.H. serum-T.S.H. rose. The patients, however, fell into two distinct groups. In eight, T.S.H. responses were in the normal range but at its extreme lower limit.[29,30] Two, starting from undectable baseline levels, demonstrated even smaller increments. In this small series of patients no regular relationship was apparent between previous psychotropic drug experience and T.S.H. response.

Before and after T.R.H. and saline injections, we obtained blood for assay of T4 iodine and T3 resin uptake. The product of each pair of determinations can be called the thyroxine index as it is proportional to free thyroxine as determined by other means.[31] Table II shows that our patients were euthyroid by this criteria but tended toward the hypothyroid side of average. T.R.H. injection caused no more increment in the thyroxine index than did saline (saline data not shown).

After completion of the clinical work, serum-total-T3 analysis became available to us. From five patients we had deep-frozen sufficient serum to provide useful information. T.R.H. had no effect on serum-T3 (table II).

Neither on injection days nor at other times did T.R.H. or saline affect ankle-reflex time.

Thus four lines of evidence lead to the conclusion that depressed women experience less of a thyroid-hormone increment after 600 μg. T.R.H. than normal men do after 100 μg.[32]

Possible relationships between clinical and chemical changes were a focus of interest. For each patient we determined the peak T.S.H. rise and the maximum decrement on the 100 mm. line test during the 6 hours after T.R.H. injection. These measures showed significant correlation ($P<0.01$, Spearman rank order). The relationship between T.S.H. response to T.R.H. and clinical response to saline (on another occasion) was random.

Discussion

We must attempt to account for two main findings—the poor T.S.H. response of our patients to T.R.H. and the apparent antidepressant effect of T.R.H. injections.

The most obvious explanation for a diminished T.S.H. response to administered T.R.H. is primary hyperthyroidism. An excess of circulating thyroid hormones exerts an increased negative feedback on pituitary T.S.H. synthesis [33] and less of this substance is available for release by T.R.H. However, we had plenty of evidence that our patients were euthyroid and no evidence whatever that they were hyperthyroid. T.S.H. response may have been blunted by previous psychotropic drug experience. However, group-B patients, who were drug-free 7 days longer than group-A patients and a total of at least 14 days, showed no greater response.

Deficient T.S.H. response could occur on another basis, from deficient endogenous tonic T.R.H. stimulation. This has been shown in animals.[34] Although our findings offer no direct evidence for hypothalamic underactivity in depression, such evidence exists. During depression patients are more resistant to the hypoglycæmic effects of insulin than after recovery.[35,36] Furthermore, Sachar et al.[37] have shown that depressed patients have a diminished growth-hormone output in response to hypoglycæmia.

TABLE II—EFFECTS OF T.R.H. INJECTION ON T.S.H., THYROXINE INDEX, AND SERUM-T3 (MEANS ± S.E.M.)

—	No.	Minutes after injection:									24 hr.
		−30	0	15	30	45	60	90	120	180	
T.S.H. (μU./l.)	10	2·3 ±0·4	2·7 ±0·5	9·2 ±1·5	12·1 ±1·8	10·2 ±1·6	7·8 ±1·2	6·0 ±1·1	5·0 ±1·3	3·8 ±1·0	..
Thyroxine index	10	5·0 ±0·4	4·4 ±0·2	..	..	..	4·8 ±0·2	5·0 ±6·3	..	..	5·0 ±0·5
T3 (ng./100 ml.)	5	..	117·2 ±4·3	..	..	..	112·4 ±19·7	120·0 ±11·4	..	..	98·2 ±15·5

If the hypothalamus is underactive in depression, how does a hypothalamic hormone exert an antidepressant action? A correlation between antidepressant effect and T.S.H. response suggests that the antidepressant effect is mediated by thyroid hormones. The concept is plausible, for T3 alone seems to have antidepressant value.[38] However, T3 must be given in large doses that speed ankle-reflex time and border on frank toxicity; and our patients showed no increment in thyroid state, chemical or physiological. In any case, the antidepressant effect of T.R.H. need not be thyroid mediated, since Plotnikoff et al.[15] have shown that T.R.H. will potentiate the behaviour effects of dopa equally in intact mice and hypophysectomised mice.

Conceivably, T.R.H. may bypass the pituitary and exert a direct effect on the thyroid gland, but there is no evidence to suggest this. T.S.H. will potentiate the action of imipramine, and it is possible that endogenous T.S.H., when released after T.R.H. administration, may exert an antidepressant effect. This seems unlikely, the more so because large doses of bovine T.S.H. (given with imipramine) do not cause an antidepressant effect as rapid as the one seen in our trial.[12,13] Our patients almost certainly experienced a prolactin release after T.R.H., though this was not measured. We do not know if prolactin has an antidepressant effect or not.

We suggest that T.R.H. has a direct central effect. Consistent with this view is the fact that small amounts of radioactive T.R.H. appear in the hypothalamus of rats after intravenous injection.[39] The dopa-potentiating effects of T.R.H. and its antidepressant effect are consistent with the catecholamine hypothesis of affective disorders[40–42] in its generic sense, though Plotnikoff's data may direct attention to dopamine rather than to noradrenaline. Dose-response studies will be needed to clarify the meaning of the correlation of T.S.H. response and antidepressant response. Conceivably, a " high " (i.e., nearly normal) T.S.H. response indicates that a fixed dose of T.R.H. has increased likelihood of restoring the hypothalamus to normal levels of function.

Can T.R.H. be used repeatedly to induce lasting remission in depression? Oral T.R.H. may prove useful. The work of Staub et al.[43] suggests that the hormone given by mouth has a prolonged action. We are also interested in the possibility of T.R.H. being useful in Parkinson's disease. L-dopa (levodopa) is useful in this condition, and T.R.H. potentiates the central effects of L-dopa in mice. According to our findings, in man T.R.H. has an effect, probably central, that is compatible with L-dopa potentiation.

Papavasiliou et al.[44] have lately reported the calming and mood-enhancing action of the pineal hormone melatonin in patients with Parkinson's disease. They suggested trials of this substance in mania and depression. It seems possible that brain hormones may in future play a prominent role in the control of behavioural disorders.

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Addendum

Similar results to ours have lately been obtained by Dr. T. M. Itil (personal communication) and by Dr. A. J. Kastin and his colleagues (*Lancet,* Oct. 7, 1972, p. 740).