THYROID
Volume 6, Number 1, 1996
Mary Ann Liebert, Inc.

Does Thyroid Hormone Have a Role as Adjunctive Therapy in Depression?[1]

IVOR M.D. JACKSON

ABSTRACT

Depression is associated with abnormalities of the thyroid axis, but the role of thyroid hormone therapy is controversial. In patients presenting with depression, the thyroid status should be carefully evaluated since hypothyroidism can cause depression. Frank hypothyroidism should be treated in the usual fashion with L-thyroxine, which may reverse the depressive state. If subclinical hypothyroidism and/or autoimmune thyroiditis are present, T_3 adjuvant administration (25 μg/day) should be seriously considered in patients resistant to tricyclic antidepressant (TCA) (and probably also) serotonin selective reuptake inhibitor (SSRI) medication. The possible efficacy of adjuvant T_4 in reversing the depression of such subjects appears less than T_3. In depressed patients with TCA or SSRI resistance and no evidence of hypothyroidism, the data available do not establish the therapeutic role of T_3 in this situation. Multicenter controlled studies of T_3 adjuvant therapy are required. The possible mechanisms through which T_3 adjuvant therapy might be efficacious are discussed.

INTRODUCTION

THE FACT THAT THYROID HORMONE DEFICIENCY could lead to depression and be reversed by thyroid hormone administration was first clearly enunciated by Asher almost 50 years ago (1). The recognition of "myxeodematous madness" subsequently encouraged a number of workers to explore the therapeutic efficacy of thyroid hormone (alone) for the treatment of depressed patients without apparent hypothyroidism. The results of these studies were inconclusive (2,3). Although, as described by Asher (1), thyroid hormone is effective in treating the depression of patients who are hypothyroid, most individuals who present with depression have circulating levels of thyroid hormone within the normal range. Nevertheless both hypothyroid and depressed patients share a number of clinical features in common (4) (Table 1). Further, disturbances of the hypothalamic–pituitary–thyroid (HPT) axis are present in depression (Table 2), although it is not known whether they reflect a cause or a consequence of the disorder. These abnormalities of thyroid function do not occur in all, or even a majority, of depressed patients but are found with a frequency significantly greater than in normal subjects.

Alterations in the thyroid axis found in depression fall into four main areas:

1. There is a blunting of the TSH rise following TRH administration, an effect that occurs in 25–30% of depressed subjects but usually normalizes with resolution of the depression (5). These depressed subjects are not thyrotoxic and do not generally have the suppressed TSH response characteristic of the latter condition. However, it should be noted that many of the TRH stimulation studies undertaken in patients with depression anteceded the era of ultrasensitive TSH assays (5). Accordingly, there may be a case for revisiting the TRH stimulation test in depression utilizing the newer TSH assays.
2. Evidence for autoimmune thyroiditis is found in at least 15% of depressed patients (6) and is associated with an exaggerated response to TRH stimulation (5). In rapid cycling bipolar disease (four or more episodes of manic depression per year), the prevalence of autoimmune thyroid disease is even higher, reaching 50% in one series (7,8).
3. There are alterations in the circadian rhythm of circulating TSH. Thus there is absence of the normal nocturnal TSH surge (9), which may result in an overall diminution of thyroid hormone secretion, supporting the view that there may be a degree of functional central hypothyroidism in some patients with depression

Ivor M.D. Jackson Division of Endocrinology, Department of Medicine, Brown University School of Medicine, Rhode Island Hospital, Providence, Rhode Island 02903.

[1]Editor's Note: The view expressed in this paper should be compared with that expressed in Thyroid 5:235–239, 1995 (ref. 21).

TABLE 1. CLINICAL FEATURES COMMON TO BOTH DEPRESSION AND HYPOTHYROIDISM[a]

Appetite loss	Decreased concentration
Weight gain	Dysphoric mood (depression)
Constipation	Loss of interest or pleasure
Decreased libido	Poor memory
Sleep increase	Cognitive dysfunction
Fatigue	

[a]Adapted from Nemeroff (4).

(9). Of note, sleep deprivation, which has an antidepressant effect, leads to restoration of the nocturnal TSH rise and an elevation in the levels of TSH and T_3 (10).

4. The most consistent abnormality of the thyroid axis is an increase in T_4 and/or free T_4 levels, though still within the conventional normal range, which regress following successful treatment of depression (8). Additionally, some patients admitted to hospital with an acute psychosis, including depression, manifest a transient elevation above normal of T_4 and/or free T_4, and occasionally TSH (11), which usually spontaneously resolves within 2 weeks without the administration of specific thyroid treatment.

EPIDEMIOLOGY OF DEPRESSION AND THYROID DISEASE

Depression, like thyroid disease, occurs most commonly in women (12). Although the peak incidence of depression in women is generally viewed as 35–45 years, there is also an increased incidence in the 50s (12), and it is becoming increasingly recognized that depressive reactions may be much more common in elderly individuals than has been hitherto appreciated (13).

Hypothyroidism occurs at all ages, with the population over 40 years of age demonstrating the highest prevalence of autoimmune thyroid disease (14). Further, up to 10% of the normal adult female population over the age of 60 years may have borderline elevation of the serum TSH—between 5 and 10 μU/mL (15). Most of these patients are asymptomatic, and they are generally not treated unless they have specific complaints or there is evidence of increased levels of circulating antithyroid antibodies (14). However, a recent report by Manzoni et al. (16) suggests that this borderline TSH elevation may not be entirely innocuous. These workers studied a group of 14 patients with subclinical hypothyroidism who had normal T_4 and T_3 levels but TSH values of 8.8 ± 1.5 vs. 1.1 ± 0.4 μU/nL in the controls ($p < 0.001$). Despite having no behavioral complaints, detailed neuropsychological testing revealed significant impairment of memory-related abilities as well as differences from controls on scales measuring anxiety, somatic complaints, and depressive features. These differences were corrected following thyroxine treatment. This study suggests that borderline elevation in the serum TSH may indeed reflect an underlying deficiency of thyroid hormone that could have behavioral or psychiatric effects including depression.

ADJUVANT THERAPY WITH THYROID HORMONE

Some of those reports indicating benefit from thyroid hormone as adjuvant therapy for depression may have included patients with subclinical hypothyroidism. Accordingly, in the evaluation of the role of thyroid hormone as adjuvant therapy for resistant depression, patients with borderline elevation of the TSH as well as those with positive antithyroid antibodies need to be excluded, since such subjects who demonstrate responsivity may have underlying hypothyroidism (17). Additionally, when evaluating autoimmunity, testing of the antithyroid peroxidase (anti-TPO) antibody (by sensitive immunoassay) should be undertaken rather than the less specific antimicrosomal antibody (by hemagglutination assay). Utilizing the anti-TPO determination, an increased number of depressed subjects was found to be positive (18). The responsivity of rapid cycling bipolar disease, which has a high prevalence of autoimmune thyroiditis, to pharmacologic doses of T_4 (8) may conceivably reflect successful treatment of an aberrant expression of thyroid disease.

Acceleration of the antidepressant onset of tricyclic antidepressants

The seeming involvement of the thyroid axis in depression led to studies further exploring the therapeutic role of thyroid hormone as a means of augmenting the effect of antidepressant therapy. Since the therapeutic response to tricyclic antidepressant therapy (TCA) is delayed, often as long as 4 weeks, Prange et al. (19) administered Cytomel (T_3) 25 μg/day along with imipramine, as a means of hastening the onset of the antidepressant effect. Although the test regimen produced a significant improvement within 1 week in women, though not in men, by 4 weeks no differences were evident in comparison to those subjects receiving imipramine plus placebo. Subsequently, Feighner et al. (20) were unable to confirm these findings. As recently pointed out by Joffe et al. (21) these and other studies all performed over 2 decades ago had major limitations due to small sample size and what are currently judged to be inadequate doses of antidepressants. Thus at this time, it cannot be viewed that T_3 has been established as a mode for accelerating the onset of response to TCAs.

Treatment of "resistant" depression

Approximately 25% of patients with depression fail to respond to TCAs (8) and the role of T_3 as augmentation therapy to convert TCA nonresponders to responders has aroused much interest (22). In this report, I have summarized the available data concerning its efficacy or lack

TABLE 2. DISTURBANCES OF THE HYPOTHALAMIC–PITUITARY–THYROID AXIS IN DEPRESSION

Blunted TRH response
Autoimmune thyroiditis
Absent nocturnal TSH surge
Sleep deprived TSH rise
Elevation of T_4 and/or free T_4

thereof and review possible mechanisms for thyroid hormone benefit in this disorder.

In their recent review, Joffe et al. (21) identified 11 studies over a period of 23 years (1970–1993), incorporating a total of 255 patients, in which T_3 was administered in an effort to convert TCA nonresponders to responders. In the open studies, Joffe et al. (21) described the results as showing response rates of 25–90%. However, this is somewhat misleading. For example, in the open label study by Thase et al. (23), the response rate of 25% did not differ from a matched historical comparison group receiving imipramine (a TCA) alone. Only 4 of these studies were double blind and involved a total of 62 patients. Three of them reported benefit from T_3, while the fourth (24) showed no advantage over placebo. Additionally, in a controlled trial of adjuvant T_3 with clomipramine in obsessive compulsive neurosis—a disorder that has depressive features—no advantage of T_3 in obtaining remission of the psychiatric disorder was found (25).

Although these reports *in toto* suggest that T_3 adjuvant therapy may be beneficial in a subset of TCA nonresponders—estimated at around 25% of such subjects by Nemeroff (22)—caution must be exercised in reaching this conclusion. Such reservation reflects concerns related to lack of clarification of the thyroid state. It should be noted that in the United States at this time the predominant antidepressants prescribed are the group of drugs that acts as serotonin selective reuptake inhibitors (SSRIs), which includes fluoxetine (Prozac), bupropion (Wellbutrin), sertraline (Zoloft), and paroxetine (Paxil) (26). No controlled trials of adjuvant therapy with these agents have been reported. However, there are case reports of dramatic responses to adjuvant therapy with T_3 after failing to respond to fluoxetine alone given over a 2- to 3-month period of time (27,28).

Electroconvulsive therapy is often effective antidepressant therapy when given to subjects who are unresponsive to pharmacologic agents. Preliminary studies have indicated that the addition of T_3 (50 μg/day) to ECT enhances the clinical responsivity to ECT (29).

T_3 MECHANISM OF ACTION

Most studies of thyroid hormone augmentation in depression have utilized T_3 rather than T_4. Those reports addressing this issue have found T_3 to be superior. Thus, Cooke et al. (30) reported that T_3 augmented antidepressant therapy in T_4 replaced hypothyroid subjects in a randomized controlled trial over a 3-week period of time. Further, Joffe (31) found that T_3 was significantly more effective than T_4 in depressed patients unresponsive to TCAs. Since T_4 equilibrates in tissues more slowly than T_3, treatment with T_4 for at least 6–8 weeks may be necessary to compare its efficacy with the more rapidly acting T_3. Nevertheless, as mentioned above, T_4 is effective in rapid cycling bipolar disease (8).

If T_3 is efficacious as adjuvant therapy in a subset of depressed subjects wherein T_4 possibly has less or no effect, what might be the mechanism of such a selective action? A hypothesis proposed by Joffe (31) views depression as a state of "relative hyperthyroidism" and that T_3 augmentation in euthyroid depressed subjects causes suppression of endogenous T_4 production so that less T_4 is available for conversion to T_3 in the brain. Such a hypothesis appears flawed since it would imply that T_3 adjuvant therapy does not cross the blood–brain barrier (BBB), while the evidence available indicates that T_3 uptake by the brain is enhanced relative to T_4 (32).

An alternative hypothesis, favored by this author, is that depression may be viewed as a state of relative CNS hypothyroidism (8) accompanied by systemic euthyroidism. There is much evidence that thyroid hormone is required for normal neuronal development and synaptogenesis, and its absence at a critical stage of brain development can lead to permanent brain damage (33). The T_3 receptor is widely distributed throughout the CNS, suggesting that thyroid hormone is necessary for normal brain function (34). Thus in patients with thyroid hormone resistance, a high prevalence of attention deficit hyperactivity disorder is found (34). As already discussed, frank hypothyroidism can cause a psychotic depression reversible with thyroid hormone replacement.

Since the active thyroid hormone in the brain is T_3, which is normally derived by conversion locally from T_4 due to the effect of brain Type II 5′-deiodinase (35), any mechanism that inhibited this enzyme could result in functional brain hypothyroidism. If inhibition of brain Type II deiodinase (34) occurs in depression, possibly due to cortisol (36), which is increased in this disorder, T_4 would be converted to reverse (r) T_3 by "inner ring" brain 5-deiodinase (Type III deiodinase), which can also inactivate T_3 (37). In support of such a mechanism, rT_3 levels have been reported to be increased in the CSF of unipolar depressed patients (38). Further, in the rat, administration of desipramine, a TCA, induces a marked increase in 5′-Type II deiodinase activity throughout the brain (39). In this scenario of Type II deiodinase failure, T_3 would be much more effective than T_4 in correcting brain hypothyroidism. Further, transport of T_4 across the BBB requires transthyretin as a carrier protein, which has been reported diminished in the CSF of patients with resistant depression (40). T_3, on the other hand, does not bind to transthyretin, which is therefore unlikely to be involved in its transport across the BBB. Thus there are supportive data for the concept of the efficacy of T_3 relative to T_4 as adjuvant therapy in depression (41). However, further studies are required before a recommendation for routine administration of T_3 could be made in TCA or SSRI resistant depression.

CONCLUSIONS

All patients with depression should be checked for evidence of thyroid dysfunction and autoimmune thyroiditis. Those subjects with frank hypothyroidism should be treated in the usual fashion with sodium-L-thyroxine (5). In patients with subclinical hypothyroidism (normal T_4 and borderline elevation of serum (TSH) and/or evidence of autoimmune thyroiditis, T_3 should be considered as adjuvant therapy for patients unresponsive to TCA (and probably also SSRI) therapy alone for 4–6 weeks. T_4 can also be considered in this context as an alternative to T_3, though the data for T_4 as an adjuvant in treatment of depression

are less persuasive. For other refractory depressed subjects, controlled multicenter trials are urgently required to address the role of T_3 adjuvant therapy as a means of converting TCA and SSRI resistance to responsivity. While circumstantial evidence does exist to suggest that selective brain hypothyroidism may exist in the presence of systemic euthyroidism, it is insufficient to permit a general recommendation for adjuvant T_3 in depression. The therapeutic role for T_3 in this context must be viewed as "not proven" at this time.

REFERENCES

1. Asher R 1949 Myxoedematous madness. Br Med J 22:555–562.
2. Flach FF, Celian CI, Rawson RW 1958 Treatment of psychiatric disorders with triiodothyronine. Am J Psychiat 114:841–842.
3. Feldmesser-Reiss EE 1958 The application of triiodothyromine in the treatment of mental disorders. J Nerv Ment Dis 127:540–546.
4. Nemeroff CB 1989 Clinical significance of psychoneuroendocrinology in psychiatry: Focus on the thyroid and adrenal. J Clin Psychiat 50(5, Suppl.):13–20.
5. Hein MD, Jackson IMD 1990 Clinical problems in psychiatric treatment of the medically ill. Review: Thyroid function in psychiatric illness. Gen Hosp Psychiat 12:232–244.
6. Nemeroff CB, Simon JS, Haggerty JJ, Evans DL 1983 Antithyroid antibodies in depressed patients. Am J Psychiat 142:840–843.
7. Bauer MS, Whybrow PC, Winokur A 1990 Rapid cycling bipolar affective disorder. 1. Association with grade 1 hypothyroidism. Arch Gen Psychiat 47:427–432.
8. Bauer MS, Whybrow PC 1988 Thyroid hormones and the central nervous system in affective illness: Interactions that may have clinical significance. Integr Psychiat 6:75–100.
9. Bartalena L, Placidi GF, Martino E, Falcone M, Pellegrini L, Dell'osso L, Pacchiarotti A, Pinchera A 1990 Nocturnal serum thyrotropin (TSH) surge and the TSH response to TSH-releasing hormone: Dissociated behavior in untreated depressives. J Clin Endocrinol Metab 71:650–655.
10. Baumgartner A, Graf K-J, Kurten I, Meinhold H 1990 Thyrotropin (TSH) and thyroid hormone concentrations during partial sleep deprivation in patients with major depressive disorder. J Psychiat Res 24:281–292.
11. Chopra IJ, Solomon DH, Huang T-S 1990 Serum thyrotropin in hospitalized psychiatric patients: Evidence for hyperthyrotropinemia as measured by an ultrasensitive thyrotropin assay. Metabolism 39:538–543.
12. Tucker GJ 1988 Psychiatric disorders in medical practice. In: Wyngaarden JB, Smith LH Jr (eds) Cecil—Textbook of Medicine, 18th ed. Philadelphia, W.B. Saunders, p. 2095.
13. Williams TF 1988 Management of Common Problems in the Elderly. In: Wyngaarden JB, Smith LH Jr (eds) Cecil-Textbook of Medicine, 18th ed. Philadelphia, W.B. Saunders, p. 29.
14. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS 1987 Thyroid failure in the elderly: Microsomal antibodies as discriminant for therapy. JAMA 258:209–213.
15. Cooper DS 1987 Subclinical hypothyroidism. JAMA 258:246–247.
16. Manzoni F, DelGerra P, Caraccion, et al. 1993 Subclinical hypothyroidism: Neurobehavioral features and beneficial effect of L-thyroxine treatment. Clin Invest 71:367–371.
17. Targum SD, Greenberg RD, Harmon RH, Kessler K, Salerian AJ, Fran DH 1984 Thyroid hormone and the TRH stimulation test in refractory depression. J Clin Psychiat 45:345–346.
18. Musselman DL, Porter MR, Ninan PT, et al. 1995 Thyroid autoantibodies in patients with mood and anxiety disorders. Soc Neurosci 21:1737 (abstract).
19. Prange AJ Jr, Wilson IC, Raben AM 1969 Enhancement of imipramine and antidepressant activity by thyroid hormone. Am J Psychiat 126:457–469.
20. Feighner JP, King LJ, Schukit MA, et al. 1972 Hormonal potentation of imipramine and ECT in primary depression. Am J Psychiat 128:1230–1238.
21. Joffe RT, Sokolov STH, Singer W 1995 Thyroid hormone treatment of depression. Thyroid 5:235–239.
22. Nemeroff CB 1991 Augmentation regimens for depression. J Clin Psychiat 52:21–27.
23. Thase ME, Kupfer DJ, Jarrett DB 1989 Treatment of imipramine-resistant recurrent depression: 1. An open clinical trial of adjunctive L-triiodothyronine. J Clin Psychiat 50:385–388.
24. Gitlin MJ, Weiner H, Fairbanks L, Hershman JM, Friedfeld N 1987 Failure of T3 to potentiate tricyclic antidepressant response. J Affect Dis 13:267–272.
25. Pigott TA, Pato MT, L'Heureux F, Hill J, Grover GN, Bernstein SE, Murphy DL 1991 A controlled comparison of adjuvant lithium carbonate or thyroid hormone in clomipramine-treated patients with obsessive-compulsive disorder. J Clin Psychopharmacol 11:242–248.
26. Richelson E 1994 Pharmacology of antidepressants—characteristics of the ideal drug. Mayo Clin Proc 69:1069–1081.
27. Gupta S, Masand P, Tanguarry JF 1991 Thyroid hormone supplementation of fluoxetine in the treatment of major depression. Br J Psychiat 159:866–867.
28. Joffe RT 1992 Triiodothyronine potentiation of fluoxetine in depressed patients. Can J Psychiat 37:48–50.
29. Stern RA, Steketee MC, Durr AL, Prange AJ Jr, Golden RN 1993 Combined use of thyroid hormone and ECT. Convuls Ther 94:285–292.
30. Cooke RG, Joffe RT, Levitt AJ 1992 T_3 augmentation of antidepressant treatment in T_4-replaced thyroid patients. J Clin Psychiat 53:16–18.
31. Joffe RT 1990 A perspective on the thyroid and depression. Can J Psychiat 35:754–758.
32. Pardridge WM 1979 Carrier-mediated transport of thyroid hormones through the rat blood-brain barrier: Primary role of albumin-bound hormone. Endocrinology 105:605–612.
33. Dussault JH, Ruel J 1987 Thyroid hormones and brain development. Annu Rev Physiol 49:321–334.
34. Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, Mixson J, Weintraub BD 1993 Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. N Engl J Med 328:997–1001.
35. Visser TJ, Leonard JL, Kaplan MM, Larsen PR 1982 Kinetic evidence suggesting two mechanisms for iodothyronine 5'-deiodination in rat cerebral cortex. Proc Natl Acad Sci USA 79:5080–5084.
36. Hindal JT, Kaplan MM 1988 Inhibition of thyroxine 5'-deiodination Type II in cultured human placental cells by cortisol, insulin, 3,5'-cyclic adenosine monophosphate and butyrate. Metab: Clin Exp 37:664–668.
37. Kaplan MM 1984 The role of thyroid hormone deiodination in the regulation of hypothalamo-pituitary function. Neuroendocrinology 38:254–260.

38. Linnoila M, Cowdry R, Lamberg B-A, Makinen T, Rubinow D 1983 CSF triiodothyronine (rT3) levels in patients with affective disorders. Biol Psychiat 18:1489–1492.
39. Campos-Barros A, Meinhold H, Stula M, et al. 1994 The influence of desipramine on thyroid hormone metabolism in rat brain. J Pharmacol Exp Ther 268:1143–1152.
40. Hatterer JA, Herbert J, Hidaka C, Roose SP, Gorman JM 1993 CSF transthyretin in patients with depression. Am J Psychiat 150:813–815.
41. Jackson IMD 1995 3,5,3′-Triiodothyronine adjunctive therapy in depression. J Clin Endocrinol Metab 80:2878–2881.

Address reprint requests to:
Dr. Ivor Jackson
Division of Endocrinology
Rhode Island Hospital
593 Eddy Street
Providence, RI 02903