Is the thyroid still important in major depression?

Russell T. Joffe, MD

Co-editor-in-chief, *Journal of Psychiatry & Neuroscience*, and Professor of Psychiatry, New Jersey Medical School, Newark, NJ

For more than a century, there have been rich descriptions in the clinical literature of prominent depressive symptoms in patients with thyroid disease, particularly clinical hypothyroidism.[1,2] This link between the thyroid and depression[1,2] provided optimism that study of the thyroid axis in unipolar depression would unravel the mystery of the etiology of the disorder. An enormous research effort over the last 50 years[3] failed to achieve this goal but, nonetheless, produced some important findings. First, the vast majority of patients with major depression are euthyroid.[3] Second, basal peripheral thyroid hormone levels are not particularly informative,[4] although subjects with depression have higher mean thyroxine (T4) levels compared with when they are remitted and also compared with healthy control subjects.[3–7] Moreover, significant decreases in T4 levels occur with response to various treatments, including antidepressant drugs,[3–5] electroconvulsive therapy[6] and cognitive–behavioural therapy.[7] Significant changes in triiodothyronine (T3) levels are inconsistent.[3,4] Last, one-quarter to one-third of subjects with depression will have a blunted thyrotropin response to thyrotropin-releasing hormone (TRH).[5,6] This finding is consistent with the increased T4 levels observed in depression[3,4] and suggests overactivity of the thyroid axis in depressive illness,[8] the pathophysiological significance of which remains to be clarified. Despite the consistent observations about the thyroid and depression reported in both the psychiatric and endocrine literature, interest in the thyroid as a major factor in the biology of depression has waned, and the thyroid axis has received little attention in current models of the etiology of depression.[9,10] Recent clinical and preclinical studies would suggest that the thyroid should not be overlooked.

Thyroid hormones have been shown to potentiate antidepressant response in treatment-resistant depression. This has been observed particularly for T3[11] but also for T4.[12] Although earlier studies have been criticized for methodological limitations, T3 has been shown to be effective in both open and controlled studies,[11] with both tricyclic antidepressant drugs[11] and selective serotonin reuptake inhibitors,[13–15] and has been shown to be significantly more effective than placebo in a meta-analysis of all available studies.[11] Moreover, T3 has been shown to be comparably effective to lithium, one of the standard antidepressant augmentation agents, in a small controlled trial[16]; this has also been shown in a recent report from the STAR*D sequential treatment trial, where T3 compared favourably to lithium augmentation (remission rates of 25% and 15%, respectively) in 142 patients.[15] Although T3 has not gained widespread acceptance as a treatment option, and its clinical effectiveness requires further evaluation, the current literature, notwithstanding its flaws, is persuasive that, at least in selected cases, thyroid hormones have antidepressant effects when used in conjunction with other antidepressant drugs.[11–16] Given that most patients with depression are euthyroid,[3,4] the thyroid hormone appears to have an antidepressant action that is not related to providing replacement therapy for occult thyroid disease.

Progress in understanding the mechanism of thyroid action in the brain was impeded, until the 1970s, by the belief that these hormones had limited impact on the mature brain, although they were crucial to normal brain development.[17] Subsequently, the importance of thyroid hormones to mature brain function has been demonstrated in several ways. First, the nuclear T3 receptor, the site of initiation of thyroid hormone action, is widely distributed in the brain, and the Tr-α subtype is specific to the brain.[18] Second, there are specific mechanisms for the active transport of thyroid hormone into the brain[19]; the type II deiodinase enzyme, responsible for the monodeiodination of T4 to the physiologically active hormone T3, is found only in the central nervous system.[20] T3 likely exerts its action in the brain by T3 receptor-mediated changes in gene expression,[17] although an effect on neurotransmission directly at the synapse is also plausible.[21]

Endogenous or exogenously administered thyroid

Correspondence to: Dr. Russell T. Joffe, Professor of Psychiatry, New Jersey Medical School, 185 S Orange Ave., MSB C-671, Newark NJ 07103-2714; fax 973 972-7104; joffe@umdnj.edu

Medical subject headings: thyroid; lithium; depression.

J Psychiatry Neurosci 2006;31(6):367-8.

hormones may play a role in the etiology of depression and the biology of treatment response at several points. First, the monoamine hypothesis of depression is still an important construct in understanding the biology of the disorder, in guiding research and in developing new treatments.[17,22] The thyroid hormone has complex interactions with the catecholamines,[17] whereas its effects on serotonin systems are more reproducible and suggest that thyroid hormone levels may have an inverse relation to brain serotonin function, mediated by changes in serotonin receptor sensitivity.[22] One of the current models of the etiology of depression proposes that reduced hippocampal neurogenesis is likely related to excess adrenal steroid and cytokine secretion, with consequent reductions in neurotrophic factors, such as brain-derived neurotrophic factor (BDNF).[9,10] Reduced hippocampal volume, adrenal hyperactivity and reduced serum BDNF levels have all been demonstrated in major depression,[9,10] and all antidepressant drugs appear to have a common effect in enhancing hippocampal neurogenesis.[23] Recent studies in rats demonstrate that thyroid hormones enhance neuronal plasticity,[24] increase hippocampal neurogenesis[25,26] and enhance the expression of various neurotrophins, including BDNF, either directly or through effects on monoamine receptors.[27,28] These data therefore support and may provide a potential explanation for the antidepressant effects observed for the various thyroid hormones.

Small changes in brain thyroid hormone levels may be associated with substantial changes in brain function.[17] This notion is consistent with the changes observed in thyroid hormone levels with various antidepressant treatments,[3–7] the antidepressant potentiating effect of relatively small doses of thyroid hormone[11] and the increasing database on thyroid effects on brain neurochemistry and gene expression.[24–28] The thyroid is surely not the primary cause of unipolar depression, advanced by the early endocrine literature, nor may study of the thyroid axis in depression yield robust findings, as observed for the adrenal axis. However, the evidence suggests that thyroid hormones cannot be ignored as important factors in the cascade of biological events leading to the onset of depression and to antidepressant response.

Competing interests: None declared.

References

1. Loosen PT. Hormones of the hypothalamic-pituitary-thyroid axis: a psychoneuroendocrine perspective. *Pharmacopsychiatry* 1986;19: 401-15.
2. Clinical Society of London. Report of a committee nominated December 14, 1888, to investigate the subject of myxoedema. *Trans Clin Soc Lond* 1888:21(Suppl):298-300.
3. Joffe RT, Levitt AJ. The thyroid and depression. In: Joffe RT, Levitt AJ, editors. *The thyroid axis and psychiatric illness*. Washington: American Psychiatric Press; 1993. p.195-253.
4. Bauer MS, Whybrow PC. Thyroid hormones and the central nervous system in affective illness: interactions that may have clinical significance. *Integr Psychiatry* 1988;6:75-100.
5. Kirkegaard C, Faber J. Altered serum levels of thyroxine, triiodothyronines and diiodothyronines in endogenous depression. *Acta Endocrinol (Copenh)* 1981;96:199-207.
6. Kirkegaard C, Faber J. Influence of free thyroid hormone levels on the TSH response to TRH in endogenous depression. *Psychoneuroendocrinology* 1986;11:491-7.
7. Joffe R, Segal Z, Singer W. Change in thyroid hormone levels following response to cognitive therapy for major depression. *Am J Psychiatry* 1996;153:411-3.
8. Joffe RT, Sokolov STH. Thyroid hormones, the brain and affective disorder. *Crit Rev Neurobiol* 1994;8:45-63.
9. Duman RS. Depression: a case of neuronal life and death? *Biol Psychiatry* 2004;56:140-5.
10. Duman R, Malberg J, Nakagawa S, et al. Neuronal plasticity and survival in mood disorders. *Biol Psychiatry* 2000;48:732-9.
11. Aronson R, Offman HJ, Joffe RT, et al. Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch Gen Psychiatry* 1996;53:842-8.
12. Baumgartner A. Thyroxine and the treatment of affective disorders: an overview of the results of basic and clinical research. *Int J Neuropsychopharmacol* 2000;3:149-65.
13. Agid O, Lerer B. Algorithm-based treatment of major depression in an outpatient clinic: clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. *Int J Neuropsychopharmacol* 2003;6:41-9.
14. Iosifescu DV, Nierenberg AA, Mischoulon D, et al. An open study of triiodothyronine augmentation of selective serotonin reuptake inhibitors in treatment-resistant major depressive disorder. *J Clin Psychiatry* 2005;66:1038-42.
15. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T3 augmentation following two failed medication treatments for depression: a STAR*D report. *Am J Psychiatry* 2006;163:1519-30.
16. Joffe RT, Singer W, Levitt AJ, et al. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry* 1993;50:387-93.
17. Henley WN, Koehnle TJ. Thyroid hormones and the treatment of depression: an examination of basic hormonal actions in the mature mammalian brain. *Synapse* 1997;27:36-44.
18. Thompson CC, Weinberger C, Leebo R, et al. Identification of a novel thyroid hormone receptor expressed in the mammalian central nervous system. *Science* 1987;237:1610-4.
19. Schreiber G, Aldred AR, Jaworowski A, et al. Thyroxine transport from blood to brain via transthyretin synthesis in choroids plexus. *Am J Physiol* 1990;258:R338-45.
20. Visser TJ, Leonard JL, Kaplan MM, et al. Kinetic evidence suggesting two mechanisms for iodothyronine 5'-deiodination in rat cerebral cortex. *Proc Natl Acad Sci U S A* 1982;79:5080-4.
21. Dratman MB. On the mechanism of action of thyroxin, an amino acid analog of tyrosine. *J Theor Biol* 1974;46:255-70.
22. Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Mol Psychiatry* 2002;7:140-55.
23. Malberg J, Eisch AJ, Nestler EJ, et al. Chronic antidepressant treatment increases neurogenesis in adult hippocampus. *J Neurosci* 2000;20:9104-10.
24. Calza L, Aloe L, Giardino L. Thyroid hormone-induced plasticity in the adult rat brain. *Brain Res Bull* 1997;44:549-57.
25. Desouza LA, Ladiwala U, Daniel SM, et al. Thyroid hormone regulates hippocampal neurogenesis in the adult rat brain. *Mol Cell Neurosci* 2005;29:414-26.
26. Ambrogini P, Cuppini R, Ferri P, et al. Thyroid hormones affect neurogenesis in the dentate gyrus of the adult rat. *Neuroendocrinology* 2005;81:244-53.
27. Vaidya VA, Castro ME, Pei Q, et al. Influence of thyroid hormone on 5-HT(1A) and 5-HT(2A) receptor-mediated regulation of hippocampal BDNF mRNA expression. *Neuropharmacology* 2001;40:48-56.
28. Giordano T, Pan JB, Casuto D, et al. Thyroid hormone regulation of NGF, NT-3 and BDNF rna in the adult rat brain. *Brain Res Mol Brain Res* 1992;16:239-45.