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Mini-Review

Pathophysiology and Clinical Features of Neuropsychiatric Manifestations of Thyroid Disease

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Abstract

Thyroid hormones (TH) have a cardinal role in the development of the central nervous system during embryogenesis and early infancy. However, the TH-responsive genes in the developing brain cease to respond to TH in adulthood. Nevertheless, thyroid dysfunction in adults is commonly associated with a host of cognitive and psychiatric problems. Cognitive decline, dysphoria, and depression are common manifestations of overt hypothyroidism while hyperthyroidism can cause agitation, acute psychosis, and apathy, especially in older people. Whereas levothyroxine treatment can reverse dementia in the setting of hypothyroidism, the effect of levothyroxine on depressive symptoms in subjects with subclinical hypothyroidism is controversial. The use of supraphysiologic doses of TH to treat depression refractory to antidepressant remains a viable therapeutic tool with the caveat that excessive doses of thyroid hormone to treat depression may have potentially damaging effects on other organ systems. The present communication describes the pathophysiology of neuropsychiatric manifestations of thyroid disease, including changes in neurotransmission, alterations in neuronal or glial cell gene expression, blood-brain barrier dysfunction, increased risk of cerebrovascular disease, and occasionally cerebral inflammatory disease in the context of autoimmune thyroid disease. Elucidating the molecular mechanisms of TH effect on cerebral tissue will help identify novel therapeutic targets for managing people with neuropsychiatric disorders.

Key Words: thyroid, depression, dementia, subclinical thyroid disease

Abbreviations: BBB, blood-brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; DIO1, deiodinase 1; FT4, free thyroxine; Glut-1, glucose transporter 1; HDRS, Hamilton Depression Rating Scale; LDAEP, loudness dependence of auditory evoked potentials; MCT, monocarboxylate transporter; MMSE, Mini-Mental State Exam; Nat-1, N-acetyltransferase-1; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormones; THRSP, thyroid hormone responsive protein; TPOAb, thyroid peroxidase antibody; TSH, thyrotropin (thyroid stimulating hormone).

Thyroid hormones (TH) have a cardinal role in the development of the central nervous system (CNS) during embryogenesis and early infancy [1]. During these early stages of life, a number of genes show robust changes in response to TH [1]. However, those TH-responsive genes in the developing brain cease to respond to TH in adulthood. Nevertheless, thyroid dysfunction in adults is commonly associated with a host of cognitive and psychiatric problems [2-6]. The pathophysiology of the TH-related changes in the cerebral tissue is diverse and includes changes in neurotransmission, alterations in neuronal or glial cell gene expression, blood-brain barrier (BBB) dysfunction, increased risk of cerebrovascular disease, and occasionally cerebral inflammatory disease in the context of autoimmune thyroid disease (Fig. 1).

The aim of this communication is to review the cognitive and psychiatric changes observed in people with thyroid dysfunction and to describe the biochemical and physiological changes that occur in the cerebral tissue in response to TH.

Methods

Literature was retrieved from a search of the PubMed database for articles written in the English language using the search terms *thyroid*, *hypothyroidism*, *hyperthyroidism*, *TSH*, or *thyroxine* AND *central nervous system*, *brain*, *affective disorder*, *depression*, *mood*, *cognitive impairment*, *dementia*, *neuropsychiatric*, *transport*, *biomarker*, *gene*. Bibliographies of these citations were also reviewed. The references were selected based on the experience and judgment of the authors. The references selected based on subjective measures (ie, judgment of authors) might have introduced bias and the authors recognize this.

Clinical Aspects of Thyroid-Related CNS Changes

Neuropsychiatric Manifestations

Clinical thyroid dysfunction is frequently associated with cognitive and psychiatric disorders [2-8] (Table 1). Cognitive decline, dysphoria, and depression are common manifestations of overt hypothyroidism while hyperthyroidism can cause agitation, acute psychosis, and apathy, especially in older people [7].

Reversible dementia is common in the setting of hypothyroidism, as exemplified by improvement of neurocognitive impairments with levothyroxine treatment [6]. Whether mild changes in plasma TH levels may increase risk of cognitive decline is still debatable. In some observational studies, subclinical hyperthyroidism (ie, decreased serum thyroid stimulating hormone [TSH] with normal free thyroxin [FT4] and

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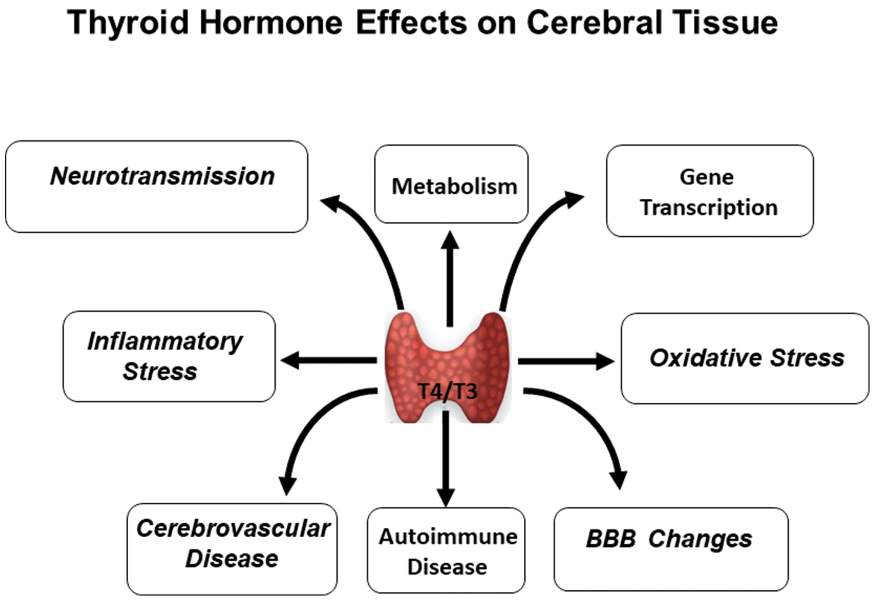

Figure 1. Thyroid hormone effects on cerebral tissue.

Table 1. Major neuropsychiatric manifestations of thyroid disease

I. Hypothyroidism	a) Cognitive decline b) Memory loss c) Dementia d) Dysphoria e) Depression f) Coma
II. Hyperthyroidism	a) Agitation b) Apathy c) Mania d) Delusional behavior e) Hallucinations f) Acute psychosis g) Dementia
III. Autoimmune Hashimoto encephalopathy	a) Personality changes b) Memory loss c) Delusional behavior d) Dementia e) Seizures f) Ataxia g) Aphasia h) Hallucinations i) Coma

free triiodothyronine [FT3] levels) and subclinical hypothyroidism (ie, normal FT4 and TSH < 10 mIU/L and more than the upper limit of the normal reference range) were found to be associated with alterations in cognitive function [9, 10]. It is noteworthy that in older people the prevalence of diagnosed subclinical hypothyroidism is 10%. However, this diagnosis may be overutilized in older age groups [9]. The prevalence of subclinical hyperthyroidism is 2.4% and may be as high as 4.3% in those who are 80 years old or older [9].

Subclinical hypothyroidism in people younger than 65 years may be associated with cardiovascular disease, stroke, and vascular dementia [11-13]. However, in people over the age of 75 years, there does not seem to be significant clinical sequelae of subclinical hypothyroidism [14-17] except possibly depression [18]. Indeed, mild TSH elevation in older adults aged 85 years or older was associated with longevity [16, 17], while higher levels of serum T4 were associated with increased mortality [16].

A cross-sectional study by Ojala et al in 335 older subjects (75 years and older) did not find an association between modestly elevated TSH concentrations (up to 10 mIU/L) and cognitive decline [15]. Similarly, in a study of 559 Dutch individuals aged 85 through 89 years, subclinical or overt hypothyroidism was not associated with either depressive symptoms or impaired physical and cognitive function [16]. There may be a gender-specific association of both low and high-normal TSH concentrations with mild cognitive impairment in otherwise euthyroid participants [5]. Women with high-normal TSH concentration might be at higher risk of cognitive decline [5].

Hippocampal memory defect in subclinical hypothyroidism is manifested as spatial and verbal memory deficits that can be reversed with thyroxine replacement [6]. The age specificity of this observation was not addressed in this study as the number of subjects studied was small (hypothyroid [n = 21] and subclinical hypothyroidism [n = 17]) [6]. However, individuals older than 60 years with TSH levels lower than 10 mIU/L do not appear to have significantly reduced cognitive function [19-21]. In a meta-analysis of 13 studies, a significant risk of cognitive impairment was observed in individuals with subclinical hypothyroidism who were younger than 75 years of age [14]. The limitations of the studies included in this meta-analysis were potential misdiagnosis of subclinical hypothyroidism in older individuals and use of TSH reference ranges that were not age specific [14]. Overdiagnosis of subclinical hypothyroidism in older individuals can lead to inappropriate intervention with thyroxin replacement [22].

The recent literature seems to indict mild thyrotoxicosis with advancement of dementia. Subclinical hyperthyroidism was associated with cognitive decline in some but not all studies [23-25]. In one study, 313 euthyroid participants with a mean age of 72.5 and no history of dementia at baseline were evaluated over a 5-year follow-up period. Subjects were categorized, based on changes in cognitive function, into a

non-progression group (n = 259) and a progression group (n = 54) who showed progressive decline in cognition or emergence of dementia [24]. The baseline TSH levels were lower in the progression group than in the non-progressing group and for every 1 mIU/L decrease of baseline serum TSH levels, there was a 1.7 times higher risk of progression of cognitive impairment after a 5-year follow-up period [24]. In another study of patients with subclinical hyperthyroidism during suppressive treatment with levothyroxine for postablative management of differentiated thyroid carcinoma, a battery of neuropsychological tests, including the Wisconsin Card Sorting Test (WCST), the Oral Word Association Test (OWAT), Trail Making Test, The Stroop Color-Word Interference test, and Digit Span test, were used to evaluate cognitive function [25]. The executive functions, psychomotor speed, and attention were significantly lower in those with subclinical hyperthyroidism. There were no differences in the results of Stroop test and Digit Span forward and backward between patients and comparison group. The intensity of depressive symptoms negatively correlated with a number of completed categories on the WCST and OWAT [25]. These observations were not supported in a study of long-term TSH suppressive therapy (at least 5 years) in 50 people aged 65 years or older with history of differentiated thyroid carcinoma, who did not show any deterioration in Mini-Mental State Examination (MMSE) scores compared with 90 control subjects [26]. It is noteworthy that MMSE is not as sensitive a test for cognitive function as the battery of neuropsychological tests included in the previous study.

In an interventional study of the association between cognitive impairment assessed by the MMSE and low-normal serum TSH in older subjects, blocking TH production with methimazole treatment prevented the decline in MMSE scores while the untreated subjects with lower TSH had the greatest reduction in MMSE scores [27] (NCT01849861). It appears that modestly increased TH levels may have adverse effects on cognition. This notion is consistent with laboratory studies showing that TH have cytotoxic effects in primary neuronal and PC 12 cells in cultures [28, 29].

Although clinically overt thyroid dysfunction can alter cognitive function, the evidence for the adverse effects of subclinical hypothyroidism or subclinical hyperthyroidism on cognitive function is modest. Whereas dementia in the setting of overt hypothyroidism can be reversed with levothyroxine treatment [6, 20], the effect of levothyroxine treatment on depressive symptoms in subjects with subclinical hypothyroidism is controversial. There is 4-fold-increased risk of depression in individuals older than 60 years with subclinical hypothyroidism (odds ratio = 4.886; 95% CI, 2.768-8.627) [18]. Furthermore, people with depression may have a higher prevalence of hypothyroidism and thyroid peroxidase antibodies correlate with markers of depression [8]. In a study of subclinical hypothyroidism after ^{131}I-treatment of Graves disease, patients had significantly higher Hamilton Depression Rating Scale (HDRS) scores, serum TSH and thyroid peroxidase antibody (TPOAb) levels compared with euthyroid patients [30]. It is not known if the change in HDRS score was relative to the euphoria of the thyrotoxicosis that preceded the treatment. Graves eye changes and high serum TPOAb were risk factors for depression and levothyroxine treatment was beneficial for those with serum TSH levels exceeding 10 mIU/L [30].

In a randomized double-blind placebo-controlled clinical trial in 60 participants (51 females and 9 males) with subclinical hypothyroidism, the affective subscale of Beck Depression Inventory did not change after 12 weeks of treatment with levothyroxine, while somatic subscale improved in the intervention group (P value = 0.02) [31]. In a larger trial of 427 adults aged 65 years or older diagnosed with subclinical hypothyroidism, defined as the presence of elevated TSH levels (4.6-19.9 mIU/L) with FT4 within the reference range, found that depressive symptoms did not differ after 12 months of levothyroxine therapy compared with placebo [32] (NCT01853579).

The association of major affective disorders with disturbances in the hypothalamic-pituitary-thyroid (HPT) axis could be secondary to common underlying genetic variation [33]. Two variants in deiodinase 1 (DIO1) (NM_000792), including a variant in the 3′UTR of DIO1 (rs11206244), were associated with altered FT4 levels in both White and African American subjects and the rs11206244 genotype was associated with lifetime major depression in White female subjects [33]. Thus, genetic variation influencing thyroid function may be a risk factor for major depression, although the association of the 2 variants of DIO1 with depression could not be confirmed in other studies [34].

The heterogeneity of the outcomes and conclusions in the available literature on cognitive and psychiatric effects of subclinical thyroid disease is probably the result of differences in the study populations with respect to age, gender, and clinical setting and is a testament to the difficulty in evaluating the effects of mild thyroid dysfunction on the central nervous system.

The Role of Supraphysiologic TH Treatment in Refractory Mood Disorder

Although there is still controversy as to the efficacy of supraphysiologic TH treatment of mood disorders, some interventional trials support this modality of treatment in refractory cases [35-39] (NCT01528839). In a review of case reports, supraphysiologic TH treatment defined as doses of triiodothyronine (T3) > 50 mcg and thyroxine (T4) > 200 mcg was used in patients with bipolar depression with presumably no apparent thyrotoxic side effects [40]. A randomized, double-blind, placebo-controlled study found that fixed-dose levothyroxine (300 μg/d) as adjunctive therapy in bipolar depression improved HDRS scores over time. The improvement was statistically significant at week 4 of treatment (P = 0.046) but not at the end of the placebo-controlled phase (P = 0.198) [35]. In another 8-week, double-blind, randomized placebo-controlled clinical trial of 153 adults with major depressive disorder, the combination of T3 and sertraline was not superior to sertraline monotherapy in the treatment of major depressive disorder [41] (NCT00208702). In a pilot study of the efficacy and safety of paroxetine augmented with risperidone, valproate, buspirone, trazodone, or TH in 225 patients with treatment-resistant major depression, the remission rates (defined as HDRS score of 7 or less at the end of study) were 26.7% for risperidone, 48.7% for valproate, 32.6% for buspirone, 42.6% for trazodone, and 37.5% for TH. There was no statistical significance among treatment arms in remission rates or adverse events [42].

The neurobiological mechanisms underlying clinical improvement with adjunctive treatment with supraphysiologic

doses of TH is not known. One study attributed this favorable effect to modulation of function in components of the anterior limbic network [43]. In this study, cerebral glucose metabolism was assessed with positron emission tomography and [F-18] fluorodeoxyglucose before and after 6 weeks of treatment with levothyroxine (n = 15) or placebo (n = 10). Levothyroxine treatment caused a significant decline in depression scores along with a significant decrease in regional glucose metabolism ($P < 0.05$) in the left thalamus, right amygdala, right hippocampus, left ventral striatum, and the right dorsal striatum. Decreases in some regions examined were correlated with a reduction in depression scores ($P < 0.05$) [43].

Another potential mechanism of the TH augmentation of antidepressant efficacy is through an increase in serotonergic neurotransmission [44, 45]. Uhl et al investigated the loudness dependence of auditory evoked potentials (LDAEP) as a measure of central serotonergic activity and response to levothyroxine [45]. In this 6-week, double-blind, randomized, placebo-controlled study, the efficacy of levothyroxine adjunctive treatment compared to placebo was monitored in 20 patients with bipolar depression. The HDRS scores and Montgomery Asberg Depression rating Scale decreased significantly during the study. Levothyroxine treatment did not lead to an increase in response rate. There was no difference in pre- and post-treatment LDAEP between the groups, and no correlation between LDAEP and psychometric measures in the course of the study [45]. The results did not support the hypothesis that augmentation therapy with levothyroxine in bipolar depression occurs through changes in serotonergic activity.

The mechanisms of the TH augmentation of tricyclic antidepressant efficacy may be attributed to the TH enhancement of postsynaptic adrenergic receptor activity [46]. Indeed, T3 treatment of rats upregulates the number of beta-adrenergic receptors (NM_007419) in the synaptosomal membranes [47]. TH can also modulate tricyclic antidepressant activity at the level of expression of TH-responsive genes [48]. In a laboratory experiment, rats treated with the combination of T3 and amitriptyline had significantly higher novel translational repressor N-acetyltransferase-1 (Nat-1) (accession number NM_001160170; antibody number sc-398540, Santa Cruz Biotechnology, Inc., Santa Cruz, CA) expression than rats treated with T3 only or amitriptyline only [48]. Amitriptyline treatment did not alter the expression of TH-responsive mRNA or THR protein (THRSP) (accession number NM_003251; antibody number sc-393982, Santa Cruz Biotechnology, Inc.) in either control or T3-treated rats [48]. Thus, alterations in the expression of selective T3 responsive genes could be a mechanism of the TH potentiation of the therapeutic efficacy of tricyclic antidepressants.

The mechanism of action of high-dose TH in refractory mood disorders may be related to an inadequate cellular adenosine 5′-triphosphate (ATP) levels that impairs TH transport into cells leading to cellular hypothyroidism [49]. Indeed, transport of TH into cells, with possible exception of pituitary, is energy intensive and dependent on ATP [50-54], and bipolar disorders are associated with mitochondrial dysfunction resulting in low cellular ATP levels [55, 56]. This interesting hypothesis requires further testing.

Adjunctive treatment with supraphysiologic doses of TH in bipolar depression is utilized occasionally. However, the currently available evidence does not support the use of TH to enhance antidepressant response in patients with major depressive disorder.

Autoimmune Hashimoto Encephalopathy

Autoimmune Hashimoto encephalopathy is a rare neuropsychiatric disorder characterized by high levels of thyroid autoantibodies in the serum and cerebrospinal fluid (CSF) and is highly responsive to glucocorticoid treatment [57]. However, brain perfusion abnormalities have been consistently described in patients with euthyroid autoimmune thyroiditis in the absence of overt neurologic symptoms [58, 59]. This suggests the possibility that a subclinical autoimmune cerebral vasculitis may actually be rather frequent in Hashimoto thyroiditis, similarly to that observed in other autoimmune disease such as systemic lupus erythematosus. This may be consistent with subtle thyroid hormone changes along with subtle neuropsychological manifestations of euthyroid Hashimoto thyroiditis.

It is estimated that 85% of diagnosed cases with Hashimoto encephalopathy are women in their fourth or fifth decades of life. However, men with Hashimoto encephalopathy tend to have more severe neuropsychiatric manifestations [60]. Approximately 95% to 100% cases have increased serum TPOAbs, and 70% to 75% have anti-thyroglobulin autoantibodies (TGAbs). The TPOAbs may also be found in the CSF (57) and they can bind to astrocytes in the cerebellum. The anti-thyroglobulin autoantibodies recognize antigens of the cerebral vessels, and anti-thyrotropin-receptor autoantibodies bind to cortical neurons [60]. It is noteworthy that the presence of positive TPO and thyroglobulin antibodies in this variant of autoimmune encephalopathy could be coincidental.

The clinical symptoms of Hashimoto encephalopathy vary and may include headaches, personality changes, memory loss, delusional behavior, dementia, seizures, ataxia, aphasia, hallucinations, and even coma [57]. Generally, there are 2 patterns of Hashimoto encephalopathy manifestations; one is a relapsing and remitting "stroke-like" vasculitic syndrome with focal symptoms, and the other is a silent, slowly progressive derangement of cognition and psychosis [60]. Both of these subtypes commonly include movement disorders.

Given the diversity and nonspecificity of clinical symptoms, Hashimoto encephalopathy is usually a diagnosis by exclusion. In 75% to 80% of patients, CSF analysis reveals albuminocytological dissociation, suggesting a breakdown of blood-CSF barrier [57]. The overwhelming majority of patients have electroencephalographic abnormalities consisting of generalized wave slowing, delta waves, and/or epileptiform activity [60]. Inflammatory changes in the cerebral circulation can sometimes be seen on magnetic resonance imaging and can result in visual field defects, focal sensory loss, and weakness [57].

Patients with Hashimoto encephalopathy often have goiter and approximately 35% have subclinical hypothyroidism, 20% have clinical hypothyroidism, 10% are hyperthyroid and the rest are euthyroid [57, 60]. More than one-third of the cases also have other autoimmune diseases, including lupus, Sjogren's, myasthenia gravis, sarcoidosis, and autoimmune hypophysitis [60].

Compared with euthyroid TPOAb-negative patients, the euthyroid TPOAb-positive patients have a much worse physical and psychological well-being, even when their thyroid

function is normalized [57]. Higher titers of antithyroid antibodies correlate with the disease activity, and treatment with corticosteroids and possibly levothyroxine diminish the antithyroid autoantibody titers and ameliorate the symptoms of the disease [60]. It is noteworthy that the role of TH in this cerebral inflammatory disease is not established as therapies for these conditions do not usually include the use of TH and the condition is not usually treated by endocrinologists.

Pathophysiology of CNS Changes in Thyroid Disease

Cerebral Vasculature and Thyroid Hormones

The blood-brain barrier (BBB) is highly regulated by various transport proteins in order to prevent serum solutes from freely crossing into the extracellular fluid of the central nervous system. Thyroid dysfunction can alter the integrity of the BBB and cerebral vasculature (Table 2). Mutations in the TH transporters such as the monocarboxylate transporter (MCT) (putative human gene accession number U59299), large neutral amino acid transporters 1 and 2 (LAT1, LAT2) (AF104032 and AF171669, respectively), and organic anion transporting polypeptide (OATP) families result in a variety of neurocognitive disorders [61, 62]. In a study of 141 patients with primary autoimmune hypothyroidism treated with levothyroxine, polymorphisms in the OATP1C1 gene (BC022461) were associated with fatigue and depression, while there were no differences in neurocognitive functioning [62]. However, there has been a very wide and variable association with these polymorphisms and clinical disease [63].

The cerebral expression of MCT8 (NM_009197) in mice brains is highest in the choroid plexus, tanycytes, and endothelium of the BBB [61]. In the adult human brain, MCT8 is expressed in the BBB endothelium and tanycytes, but not in the choroid plexus [61]. The solute carrier family 16 member 2 (*SLC16A2*) gene encodes the MCT8, and X-linked inactivating mutations of this gene result in the Allan-Herndon-Dudley syndrome, a severe neurodevelopmental disorder manifested with psychomotor disabilities, severe intellectual disability, limb dystonia, truncal hypotonia, and muscle spasticity [61]. However, one study found that although MCT8-deficient patients had limited TH transport through the BBB, they did not consistently exhibit fatigue and depressive symptoms, as would be expected from a "hypothyroid brain" [61].

Aging may also alter the BBB transport of TH. In animal experiments, the BBB transport of levo-T3 was decreased in aging rats while the transport of dextro-T3 was not altered with age [64]. This age-related stereoselective alteration in TH transport may contribute to the CNS changes with aging. However, there are no significant changes in brain T3 content suggesting that the reduced BBB transport of T3 in aged rats is counterbalanced by a reduction in T3 clearance from the brain [64].

Hypothyroidism in rats can also alter BBB transport of some nutrients. In hypothyroid rats maintained on methimazole, the brain uptake of beta-hydroxybutyrate was significantly reduced while hypothyroid rats treated with TH replacement had normal brain uptake of beta-hydroxybutyrate [65]. The BBB transporters of hexoses, neutral amino acids, basic amino acids, and monocarboxylic acids were not altered in hypothyroid rats [65]. Although the BBB transport of hexoses was not altered in hypothyroid rats, 55 kDa solute carrier family 2 member 1 (Slc2a1, also known as glucose transporter 1 [Glut-1]) (accession number NM_138827; antibody number 07-1401, Millipore Sigma, Burlington, MA) in cerebral tissue measured with immunoblotting was decreased in hypothyroid young rats [66]. The cerebral tissue 55 kDa Glut-1 content was not altered in hyperthyroid young rats but was increased in aged rats compared to euthyroid aged rats. The 45 kDa isoform of Glut-1 in rat cerebral tissue did not significantly change with age or thyroidal state [66]. The Glut-1 content can alter glucose metabolism and may contribute to the neuropathology in thyroid dysfunction [66].

Another facet of TH effects on cerebral vasculature is related to the TH effects on cardiovascular disease. In a systematic review and meta-analysis, there was an increased risk of stroke events and fatal stroke in hypothyroid patients aged 18-64 compared with euthyroid patients, but no increased risk in patients 65 years old and over [11]. Hypothyroidism, both subclinical and overt, is associated with a hypocoagulable state, potentially explaining the higher risk of hemorrhagic stroke events in younger patients with subclinical hypothyroidism. In addition, TH have significant effects on vascular resistance and cardiac contractility. Decreases in cardiac output in hypothyroid state reduces cerebral perfusion, thereby aggravating the risk of neurocognitive disorders. Subclinical or clinical hypothyroidism is associated with increased plasma levels of atherogenic lipids and hypertension thus increasing the risk of stroke and cardiovascular disorders [11, 67]. Salutary effects of levothyroxine treatment on cardiovascular outcomes were demonstrated in a study of 162 369 patients with hypothyroidism on thyroid replacement therapy [68]. Longitudinal TSH measurements from diagnosis to outcomes, study end, or loss to follow-up (n = 863 072) were included in the analysis. Compared with the reference TSH category (2-2.5 mIU/L), risk of ischemic heart disease and heart failure increased at high TSH concentrations (>10 mIU/L) (hazard ratio [HR] 1.18; $P = 0.03$ and HR 1.42; $P < 0.001$, respectively). The risk for stroke/transient ischemic attack was marginally reduced at TSH concentrations of 3 to 3.5 mIU/L (HR 0.86; $P = 0.04$) and 4 to 10 mIU/L (HR 0.90; $P = 0.05$) Increased mortality was observed in both the lowest and highest TSH categories [68].

Table 2. Hypothyroidism-related changes in cerebral vasculature

I. Cerebral vessels	a) Decreased cerebral blood flow in hypothyroidism. b) Increased risk of stroke as a result of increased atherogenic lipids and hypertension.
II. Blood-brain barrier	a) Decreased transport of beta-hydroxybutyrate. b) Unaltered transport of hexoses, neutral amino acids, basic amino acids, and monocarboxylic acids. c) Decreased responsiveness of β-adrenergic receptor number and activity in cerebral microvessels.

Biochemical Effects of TH in the Adult Brain

Thyroid hormone and its receptors of both alpha (NM_00131983) and beta (NM_001113417) subtypes are abundant within the cerebral tissue [69, 70] and modulate neurotransmission and gene expression. Several genes have

been identified as targets of TH action during embryogenesis (Table 3) [71-74]. In contrast, there is paucity of genes identified to be responsive to TH in adulthood [75-79]. The paucity of TH-responsive genes in adult cerebral tissue suggests that the adult brain is poorly responsive to TH or the effect of TH on adult cerebral cortex is either posttranscriptional or initiated at sites other than nuclear receptors. An example of the latter is the effect of TH on adrenergic neurotransmission [46]. Thyroid hormones increase β-adrenergic receptor number and increase the responsiveness of β-adrenergic receptor activity in synaptosomal membranes and cerebral microvessels [47, 80].

Thyroid hormone can cause cell death in primary neuronal cultures and in PC12 cells [28, 29]. Thyroid hormone responsive protein (THRSP) (NM_003251) may mediate this effect [28, 29]. Cell culture studies indicate that T3 can increase the expression of THRSP, while exogenously expressed THRSP, through transfecting neuronal or PC 12 cells with pSVL-THRSP, causes cell death [29]. However, expression of exogenous THRSP in the colonic epithelial cell line Caco-2 and the glial cell line U251 has no effect on cell viability [29]. The form of cell death is predominantly necrosis although cell cycle arrest may also occur. This effect of THRSP on cell viability is not modulated by c-Abl tyrosine kinase [81].

Another novel gene identified as TH responsive in adult rat cerebral tissue is the novel translational repressor N-acetyltransferase-1 (Nat-1) (NM_001160170) [79]. The responsiveness of this gene to TH was identified through reverse transcriptase-polymerase chain reaction differential display. The Nat-1 mRNA is widely expressed in various tissues, and in hepatic tissue, it is also TH responsive. There is a significant reduction in TH responsiveness of THRSP and Nat-1 in senescent rats [79, 82].

In a study to identify genes in the adult rat brain that are regulated by TH, the Affymetrix (Santa Clara, CA) U34N rat neurobiology microarray was used [83]. This microarray contains probes for 1224 neural-specific genes. Changes in gene expression were considered significant only if they were observed by Northern blot analysis as well. Hyperthyroidism was associated with modest changes in the expression of only 11 genes [83]. The expression levels of 8 genes were increased by T3 treatment. These genes were the ectonucleotide polynucleotide pyrophosphatase/phosphodiesterase 2 (*Enpp2*) (NM_057104), myelin oligodendrocyte glycoprotein (*Mog*) (NM_022668), microtubule-associated protein 2 (*Map2*) (NM_001039934), growth hormone (*Gh*) (NM_008117), Ca^{2+}/calmodulin-dependent protein kinase II β (*Camk2β*) (NM_001220), Purkinje cell protein 4 (*Pcp4*) (NM_013002), a sodium-dependent neurotransmitter (S56141), and the myelin-associated glycoprotein (*Mag*) (NM_017190). Three genes were suppressed by T3 treatment, including the activity and neurotransmitter-induced early genes-1 and -7 (*Ania-1* and *Ania-7*) (AF030086 and AF050659, respectively) and the guanine nucleotide-binding protein subunit β1 (*Gnb1*) (NM_030987). Despite the paucity of TH-responsive genes in adult cerebral tissue, TH appears to modulate both structural (eg, through Mog and Pcp4) and functional (eg, through Ania-1 and Ania-7) integrity of the cerebral tissue [83].

Biochemical abnormalities and thyroid dysfunction may occur early in patients with major depressive disorder. Studies using 2-dimensional multivoxel proton magnetic resonance spectroscopy in 26 first-episode, treatment-naïve patients with major depressive disorder and 13 healthy controls found that the major depressive disorder patients had a significantly lower N-acetylaspartate/creatine ratio in the left white matter in the prefrontal lobe [84]. There were no significant differences in choline containing compounds and no significant changes in the metabolite ratios in the bilateral anterior cingulate cortex and hippocampus [84]. These changes in the right prefrontal lobe white matter were positively correlated with the level of TSH but not circulating thyroid hormone levels [84]. The clinical consequences of these biochemical changes are not known.

Thyroid hormones may have a role in the pathogenesis of Alzheimer disease [85] through oxidative stress, inflammation [86, 87], and alterations in the splicing of the β-amyloid precursor protein isoforms [88]. However, daily treatment of rats with T3 does not alter the cerebral tissue content of malondialdehyde (MDA) modified proteins [89] even though the peroxidation byproducts such as ethane exhalation

Table 3. Thyroid hormone–related biochemical changes in adult brain

I. Neurotransmission	a) Hyperthyroidism causes increased β--adrenergic receptor number and activity in synaptosomal membranes and cerebral microvessels.
II. Metabolism	a) Decreased cerebral glucose metabolism in hypothyroidism. b) Decreased N-acetylaspartate/creatine ratio in the left prefrontal lobe white matter of depressed people correlate with TSH. No significant differences and choline containing compounds.
III. Gene expression	Changes in the mRNA of the following genes: Nerve growth factor (*Ngf*) (NM_013609), Neurotrophin-3 (*Ntf3*) (NM_001164034), Brain-derived neurotrophic factor (*Bdnf*) (NM_007540), Neurogranin (*Nrgn*) (NM_022029), Thyroid hormone responsive protein (THRSP) (NM_003251), Novel translational repressor (*Nat-1*) (NM_001160170); Ectonucleotide pyrophosphatase/phosphodiesterase 2 (*Enpp2*) (NM_057104), Myelin oligodendrocyte glycoprotein (*Mog*) (NM_022668), Microtubule-associated protein 2 (*Map2*) (NM_001039934), Growth hormone (*Gh*) (NM_008117), Ca(2+)/calmodulin-dependent protein kinase β subunit (*Camk2β*) (NM_001220), Purkinje cell protein 4 (*Pcp4*) (NM_013002), Sodium-dependent neurotransmitter (S56141) and the myelin-associated glycoprotein (*Mag*) (NM_017190). Three genes that are suppressed by T3 treatment, including the activity and neurotransmitter-induced early genes-1 and -7 (*Ania-1* and *Ani-7*) (AF030086 and AF050659, respectively) and the guanine nucleotide-binding protein subunit β 1 (*Gnb1*) (NM_030987).
IV. Oxidative/inflammatory stress	a) Increased risk of Alzheimer disease. b) Alterations in the splicing of the β-amyloid precursor protein isoforms. c) No change in the cerebral tissue content of malondialdehyde modified proteins.

increases [90]. The biological or clinical implications of these changes are not known, but it is tempting to speculate that the increased oxidative stress and inflammation induced with TH may promote Alzheimer's disease.

There are a myriad of biochemical effects of TH on the brain (Table 3). However, most of the studies in the literature are descriptive. Future studies should attempt to identify causal relationships between a specific biochemical perturbation in cerebral tissue and clinical manifestations of thyroid dysfunction.

Conclusions

The TH-related changes in neurotransmission, cerebral metabolism, and BBB function contribute to the neuropsychiatric syndromes associated with thyroid dysfunction. The use of supraphysiologic doses of TH to treat depression refractory to antidepressant remains a viable therapeutic tool with the caveat that excessive doses of TH to treat depression may have potentially damaging effects on other organ systems [91]. However, this modality has not gained wide acceptance mostly because of inconsistent trial results and concern for causing thyrotoxicosis associated clinical side effects. Elucidating the molecular mechanisms of TH effect on cerebral tissue will help identify novel therapeutic targets for managing people with neuropsychiatric disorders.

Disclosures

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. The known registration numbers of clinical trials, GenBank accession numbers and antibody identification were included when appropriate.

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