Association of Thyroid Dysfunction and Mood Disorders and Role of Imaging: a Review

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ABSTRACT

Thyroid hormones play a critical role in the adult brain impacting mood and cognition. Some psychiatric symptoms are produced by thyroid illnesses and there is a frequent association of thyroid dysfunction with mood disorders. It is now clear that without optimal thyroid function, mood disturbance, cognitive impairment and other phychiatric symptoms can emerge. The usefulness of adding thyroid hormones to antidepressive treatment in euthyroid patients to obtain a potentiation effect has been proved repeatedly. The most common strategy is potentiation with T_3, but high doses of T_4 have been also used in patients with resistant depression.
Brain imaging techniques evaluating cerebral metabolism, perfusion, and anatomy enabled encouraging insights into the thyroid-brain relationship. The most consistent finding in patients with hypothyroidism is global diffuse hypoperfusion more pronounced in posterior brain region or in parietal lobe. Functional MRI in patients with thyroid diseases of different length and severity could help to identify functional aberrations such as memory impairments or altered emotional processing, which has long been suggested from animal studies. Structural changes related to myelin, which have been observed in various animal models, can now be studied with quantitative T2 or quantitative magnetization transfer (MT) imaging. Diffusion tensor imaging (DTI) can reveal information on white matter integrity.

INTRODUCTION

Thyroid hormones are widely distributed in the brain and have a multitude of effects on the central nervous system (1). Some psychiatric symptoms are produced by thyroid illnesses and there is a frequent association of thyroid dysfunction with mood disorders (2). Notably many of the limbic system structures where thyroid hormone receptors are prevalent have been implicated in the pathogenesis of mood disorders (1). Thyroid hormones exert their action in the central nervous system through a variety of mechanisms: modulation of gene expression of several groups of proteins, some of them with known physiopathological implications in mood disorders and the influence over serotonin and noradrenergic neurotransmission, known to be one of the modes of action of antidepressants (2).

Hypothyroid states are associated with both functional and structural brain alterations and also seen in patients with major depression (3). Taken together overt 0.4% and subclinical 9%, hypothyroisism is prevalent in about 9.4 % of the adult population (4) and commonly affects brain function. Conversely, 15% of patients with depression display hypothyroid states including subclinical hypothyroidism (5), and about 25-30% of depressed patients show a pathological response to the thyrotropine releasing hormone (TRH) stimulation test (6).

Both hyperthyroidism and hypothyroidism are associated with changes in mood and intellectual performance; and severe hypothyroidism can mimic melancholic depression and dementia (7, 8). The neurocognitive impairments accompanying dysfunction of the thyroid gland are usually reversed rapidly following return to euthyroid hormone status, although severe hypothyroidism, if left untreated, may rarely result in irreversible dementia (9, 10). A very recent study concluded that

free thyroid hormones concentrations are associated with depression severity and have an impact on final clinical outcome. It can be more efficient to augment and accelerate the treatment of major depressive disorder with triiodothyronine instead of levothyroxine because of individual differences in thyroid hormones metabolism (11). With the rapid advances in basic science and methodological techniques over the past 25 years, however, there have been dramatic changes in the concepts of thyroid hormone action in the adult brain (12). Although no direct methods for *in vivo* measurement of brain thyroid metabolism exist, functional brain imaging techniques to evaluate cerebral blood flow and metabolism have offered some promising insights into the thyroid–brain relationship (13). Functional brain imaging studies using positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose demonstrated that thyroid hormone treatment with levothyroxine affects regional brain metabolism in patients with hypothyroidism and bipolar disorder (1).

Here, we review the relationship between thyroid hormone and neuropsychiatric symptoms in patients with primary thyroid disease and primary mood disorders as well as role of functional brain imaging in this regard.

THYROID HORMONES AND MOOD; POTENTIAL MECHANISM OF ACTION

Thyroid hormones act via genomic and non-genomic effects in the molecular level. As part of the nuclear superfamily of ligand-modulated transcription factors, thyroid hormones bind to intracellular nuclear receptors. Genomic actions of T_3 are mediated through the control and usually increase of gene expression (14, 15). Genes that are regulated by thyroid hormones are known to encode for proteins such as myelin, neurotrophins, and proteins that are involved in intracellular signaling pathways (1).

Non-genomic actions of thyroid hormones have been described in the brain and peripheral tissues. After binding to cytoplasmic thyroid hormone receptors, T_3 appears to be able to rapidly activate the phosphatidylinositol-3-kinase protein pathway and thereby achieves vasodilatory and neuroprotective effects (16). Additionally, an increase in serotonergic neurotransmission is mediated by a thyroid hormone induced reduction of the sensitivity of 5-HT1A autoreceptors in the raphe nuclei and increase in 5-HT2 receptor sensitivity (17, 18).

Thyroid hormone homeostasis in the brain underlies a complex interaction of different autoregulative mechanisms (19, 20). The activity of specific thyroid hormone transporters (MCT8, LAT2) and the carrier transthyretin determines intracellular concentration of thyroid hormones via mediating their cellular influx and efflux under consideration of overall circulating levels of T_4 and T_3 (19). The activity of deiodinases controls local bioavailability of T_3 in concert with other less understood mechanisms, e.g. the local distribution of the different nuclear thyroid hormone receptors (TRα and TRβ in diverse isoforms) (21-23). Thyroid hormone receptors are widely distributed in the brain with highest concentrations in cerebral cortex, hippocampus, amygdala, plexus choroideus and olfactory bulb (23).

Interestingly, the limbic structures, where thyroid hormone receptors are prevalent, have repeatedly been shown to be implicated in the pathogenesis of mood disorders (24). However, the neuropharmacological basis and the functional pathways for the modulatory effects of thyroid hormones on mood are yet to be understood, even though several studies revealed interactions with different neurotransmitter systems, which are generally believed to play a major role in the regulation of mood and behaviour, i.e norepinephrine or serotonine (18, 25). Other

proposed mechanisms for thyroid involvement in the aetiology of mood disorders include disturbances or reactive hyperactivity in the HPT axis, as manifested in the blunted TSH response to TRH found in some patients with depression (26-28).

BRAIN VASCULAR CHANGES IN THYROID AND MOOD DISORDERS

Thyroid hormones are known to affect the vascular system. Hypothyroidism is associated with impaired fibrinolysis and blood coagulation resulting in cerebrovascular diseases (29). There are only a limited number of recent functional imaging studies of patients with thyroid disorder. These studies include patients with hypothyroidism of varying levels of severity from autoimmunity or thyroid cancer, and generally employed single photon emission computed tomography (SPECT) or positron emission tomography (PET). The most consistent finding from studies of patients with hypothyroidism is global, diffuse hypoperfusion (30, 35). Several studies found the perfusion deficits most pronounced in posterior brain regions (31, 32, 34) or in the parietal lobe (30). In several studies, some degree of normalization of perfusion was reported when patients became euthyroid (33, 35). One study group of patients with previously untreated mild hypothyroidism showed reversible hypoperfusion in the subgenual and perigenual anterior cingulate cortex, posterior cingulate cortex, amygdala and hippocampus (35). In other studies (31, 32, 34), the hypoperfusion remained evident after initiation of the thyroxine replacement therapy, although this finding did not predict the outcome of long-term treatment (34).

Differences in the study populations may be the reason for such variable findings. Published results refer either to severe cases of hypothyroidism (30, 31) or mild cases (34, 36). Taken together the existing data it may indicate that long term and severe hypothyroidism, presumably leading to irreversible structural neuronal and vascular changes, is associated with chronic perfusion and functional alterations, which may be ameliorated by treatment but not fully restored. In contrast, shorter and milder courses of hypothyroidism, presumably not being paralleled by irreversible structural changes, seem to be more accessible to substitution treatment.

NEUROPSYCHIATRIC CHANGES IN THYROID AND MOOD DISORDERS

Disturbances of the thyroid system, particularly if leading to a hypothyroid state, may profoundly alter mental functions influencing cognition and emotions. Severe hypothyroidism may lead to both severe depression and dementia (7) especially if left untreated (9). Neuropsychologically, several cognitive defects in general intelligence, psychomotor speed, visual-spatial skills, working and long-term memory have been observed ranging from minimal to severe (37, 39). It was suggested that hypothyroid-related memory defects are not attributable to an attention deficit but rather to specific retrieval deficits (37, 40). Motor skills, language, inhibitory efficiency, and sustained attention appear to be less impacted by hypothyroidism (37, 39). Older adults were more vulnerable to cognitive changes due to hypothyroidism (39).

It is still a matter of discussion as to whether subclinical hypothyroidism is associated with cognitive impairments. A consistent finding among many studies was a specific deficit in working memory tasks (37). A functional MRI (fMRI) study by Zhu et al. (36) found that working memory was impaired in patients with subclinical hypothyroidism but not other memory functions. These impairments were reversible with L-thyroxine ($L\text{-}T_4$) treatment.

Hyperthyroidism or thyrotoxicosis is accompanied by psychiatric symptoms, including dysphoria, anxiety, restlessness, emotional lability, and impaired concentration. In elderly patients,

depressive symptoms such as apathy, lethargy, pseudodementia and depressed mood can also occur (41). Approximately 60% of thyrotoxic patients have an anxiety disorder and between 31% and 69% have a depressive disorder (42,43). However, overt psychiatric illness only occurs in approximately 10% of thyrotoxic patients (44).

THYROID HORMONES IN TREATING MOOD DISORDERS:

Because of the relationship between thyroid disease states and psychiatric symptoms, there has long been an interest in using thyroid hormones to treat mood disorders. In the 1930s, Norwegian physicians used desiccated sheep thyroid gland to treat patients with cyclic mood disorders (45). Although thyroid hormone monotherapy is not an adequate treatment for patients with primary mood disorders, since the late 1960s (46), a series of open and controlled clinical trials have confirmed the therapeutic value of adjunctive treatment with thyroid hormones in mood disorders. Specifically, there is good evidence that T_3 can accelerate the therapeutic response to tricyclic antidepressants (47) and in treatment-resistant depression; T_3 may augment the response to tricyclic antidepressants, although the results have been inconsistent (48,49). T_3 has also been shown to augment the response to sertraline (50) but not to paroxetine (51).

In a series of open-label studies, adjunctive treatment with supraphysiological doses of L-T_4 was found to be effective in the maintenance treatment of patients with severe rapid cycling or resistant bipolar disorder who did not respond to standard measures (26, 51-53). Supraphysiological L-T_4 may also have immediate therapeutic value in antidepressant-resistant bipolar and unipolar depressed patients during a phase of refractory depression (54). In these patients with malignant affective disorder, doses of 250–600 μg/day L-T_4 are required to achieve therapeutic effect, which is much higher than those used in the treatment of primary thyroid disorders. Although treatment with supraphysiological T_4 requires close monitoring, the hyperthyroxinemia is tolerated surprisingly well. No serious effects, including loss of bone mineral density, were observed even in patients treated for extended periods (49,52,55). The low incidence of adverse effects and high tolerability reported by patients with affective disorders who are receiving high-dose thyroid hormone therapy contrasts with that typically seen in patients with primary thyroid disease. For example, patients with thyroid carcinoma treated with high doses of L-T_4 to achieve suppression of TSH commonly complain of the symptoms of thyrotoxicosis. Furthermore, total thyroxine, free thyroxine, and total triiodthyronine levels in depressed patients were less elevated in response to supraphysiological doses of L-T_4 than in healthy controls (17,56). This could be explained by the hypothesis that, in unipolar depression, T_4 is to a greater extent metabolised into inactive compounds such as rT3 compared to in healthy subjects. Support for this hypothesis stems from older studies that describe elevated rT3 serum and CSF concentrations in depressed patients (57,58).

ROLE OF BRAIN IMAGING

Principal brain imaging techniques mentioned in this article are single photon emission computed tomography (SPECT), positron emission tomography (PET), and different methods of magnetic resonance imaging (MRI). PET and SPECT are nuclear imaging methods that require the injection of radioactive tracers into the circulatory system. Those tracers bind to molecular structures like transporters and receptors in the human brain. Measuring of the local distribution of the bound tracers allows an estimation of regional brain activation or availability of receptors (3).

In contrast to these nuclear imaging methods, MRI is non-invasive and uses magnetic fields and radio waves instead of ionizing radiation. Structural MRI methods allow creating images of anatomical

structures in an excellent spatial resolution (less than 1 mm). Diffusion tensor imaging (DTI) characterizes the mobility of water molecules and, thus, the directionality and integrity of white matter tracts. Magnetization transfer (MT) is sensitive to myelin content and is therefore useful in detecting early demyelination processes. Functional magnetic resonance imaging (fMRI) has become the tool of choice to study functional aspects of the human brain. This method detects local increases of blood flow and the following decrease of deoxygenated hemoglobin during task related brain activity. The signal measured directly relies on the so-called BOLD (blood oxygen level dependent) effect. It is based on the different magnetic properties of oxygenated and deoxygenated hemoglobin. The origin of the BOLD signal is still a matter of discussion as it is also based on the complex interaction of neuronal metabolism, neuronal activity, blood flow and blood volume. Nevertheless fMRI enables the monitoring of active neuronal networks during the performance of specific paradigms, e.g. a memory task. Related to affective disorders, MRI allows the investigation of functional and structural deficits associated with neuropsychiatric symptoms as well as treatment effects (3).

Major advantages of neuroimaging methods are that brain structure and function as well as molecular and neurochemical processes can be studied in the living human. An important limitation of the mentioned brain imaging techniques refers to temporal resolution. While neuronal activities occur in the range of milliseconds, processes detected by imaging methods currently ranges between seconds (fMRI) and minutes (PET). Additionally, all methods measure brain activity indirectly through changes in blood flow or glucose uptake. Consequently, alterations in baseline perfusion and metabolic rate of oxygen may affect the results (3).

CONCLUSION

Thyroid hormones play a critical role in the metabolic activity of the adult brain, and neuropsychiatric manifestations of thyroid disease have long been recognized. It is now clear that without optimal thyroid function, mood disturbance, cognitive impairment and other psychiatric symptoms can emerge.These neuropsychiatric impairments are generally reversible following return to euthyroid status, although some defects may persist in a subset of patients. In patients with primary mood disorders, thyroid hormones appear to be capable of modulating the phenotypic expression of their illness. The adjunctive use of supraphysiological doses of L-T_4 in malignant affective disorders frequently provides remission without adverse physiological effects where all other treatments have failed. However, it is only recently that methodology such as functional neuroimaging has been available to facilitate investigation of thyroid hormone metabolism in brain and functional MRI has become the pioneer in this regard.

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