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Thyroid Axis Activity in Depression

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Abstract

It has long been known that both excess and insufficient thyroid hormones can lead to depression. Nevertheless, the vast majority of depressed patients have thyroid function tests within the euthyroid range-albeit it has been described subtle alterations such as a slight elevation of serum Thyroxine (T4) and/or low Triiodothyronine (T3) levels. Many studies suggest that major depression is associated with subtle chronobiological Hypothalamic-Pituitary-Thyroid (HPT) axis dysfunction. The most consistent abnormality in euthyroid depressed patients is blunting of the Thyrotropin (TSH) response to morning injection of Protirelin (TRH). For chronobiological reasons TRH induced TSH stimulation is higher in the evening at 11 PM (where TSH reaches its nyctohemeral peak) than at 8 AM, and the difference between 11 PM and 8 AM TRH-TSH response (i.e., ΔΔTSH) represents a very sensitive chronobiological index. This test, correlated with the nyctohemeral secretion of TSH, is reduced in about 70% of inpatients with major depression and is normalized with successful antidepressant treatment. This normalization appears related to clinical response rather than an intrinsic effect of the antidepressant on the HPT axis. On the other hand, thyroid hormones can be an effective adjunct to antidepressant treatment, while limited data are available on long-term safety. Finally, the development of TRH analogs, by reinforcing the homeostatic modulatory systems, could represent an area of striking opportunity in the treatment of mood disorders, especially in patients with suicidal ideation.

Keywords: TRH; TSH; T4; T3; Antidepressants; Depression; Suicide

Introduction

The occurrence of mental disorders, especially of mood, during thyroid affections has been known for over a century. The frequent association between dysthyroidism (hyper- and hypothyroidism) and mood disorders (uni- or bipolar) led to the hypothesis that thyroid hormones could play a role in the regulation of mood and therefore may be involved in the pathophysiology of affective disorders. However, the vast majority of depressed patients have thyroid function tests within the euthyroid range, albeit it has been described subtle alterations such as a slight elevation of serum thyroxine (T4) and/or low triiodothyronine (T3) levels (although still within the normal range) [1]. While euthyroid, most patients exhibit a chronobiological Hypothalamic-Pituitary-Thyroid (HPT) axis dysregulation (i.e. loss of the nocturnal Thyrotropin [TSH] rise [2-4], blunted evening TSH response to protirelin [TRH], reduced difference in TSH response between 11 PM and 8 AM TRH tests [ΔΔTSH] [5]), possibly associated with blunted 8 AM-TSH response to TRH and/or altered levels of circulating thyroxine (total and/or free [FT4]) and triiodothyronine (FT3 and/or free [FT3]) [1].

For practical reasons, the TRH test is usually performed in the morning, but its clinical value is limited because of its modest diagnostic sensitivity. Owing to the circadian activity of the thyrotrophs, which is maximal between 11 PM and 1 AM, pituitary TSH secretion is more sensitive to TRH stimulation in the evening than in the morning, both in normal controls and in depressed patients [5]. In 1990 our group, reported that the 11 PM TRH-TSH test was more sensitive than the 8 AM TRH-TSH test, and that the difference in TSH response between 11 PM and 8 AM TRH tests (ΔΔTSH) was an even more sensitive measure [5]. The ΔΔTSH test represents a very sensitive chronobiological index and is reduced in about 70% of inpatients with major depression.

In this article, we will present an overview of the HPT axis investigations in depression, and the applications in three different contexts : 1) clinical, as a state marker of depression and suicidal behavior; 2) pathophysiological, since according to the history of suicidal behavior central TRH secretion might be increased (in patients without such a history), normal (in patients with suicidal behavior disorder in early remission) or decreased (in depressed patients with current suicidal behavior disorder)-supporting the notion that TRH might act as a homeostatic compensatory mechanism; and 3) therapeutic, since: altered 11 PM-ΔTSH at baseline augurs poorer response to subsequent Antidepressant Treatment (ADT), chronobiological restoration of the HPT axis activity precedes clinical remission, and alteration of the HPT axis during ADT is associated with treatment resistance. Finally we will discuss the use of thyroid axis hormones in the treatment of mood disorders.

Clinical Applications

In depression TSH basal and thyroid hormone, values are generally within the normal range. One may note that the "one sampling strategy" is hindered by the fact that plasma hormone concentration reflects the interaction of several related rhythmic variables like hormone synthesis, secretion, transport and metabolism, and will vary according to the stage of each variable at the time of measurement. Repeating sampling appears preferable in order to take into account chronobiological variations. Thus, it has

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been consistently found that circadian TSH secretion is altered in depression (i.e. failure of the normal nocturnal surge of TSH, and lower and less variable 24-hour TSH levels compared to controls [3-6]. However, to be valid such chronobiological approaches require a synchronization of the patients' environments, since many factors, both internal and external (i.e., "masking" factors), can influence biological rhythms. These stringent experimental protocols can only be performed in hospital. Moreover, there is no threshold defining an abnormal profile for a given patient, this consequently limits the potential applications in the field of "personalized medicine".

The advantage of the TRH test over static ("unstimulated") investigations is to assess the functionality of the HPT axis by destabilizing the homeostatic balance. However, the sensitivity of the TRH test depends of the dose administered (200 µg iv is more suitable than 500 µg iv to assess the sensitivity of the pituitary TRH receptors) and the time of the day. In the morning the sensitivity is modest: the 8 AM TRH-TSH test is blunted in about 25% of depressed patients (for review see [1]). For chronobiological reasons, the 11 PM TRH-TSH test is blunted in about 40% of depressed inpatients. ΔΔTSH values, which are strongly correlated with 11 PM-ΔTSH values [7], are reduced in about 70% of depressed inpatients [8].

Although decreased ΔΔTSH values are independent of age, sex, intensity of depressed symptoms, and polarity of depression (i.e. bipolar/unipolar), the history of suicidal behavior appears to be closely linked to the HPT axis activity. In depressed patients without a history of suicidal behavior TSH responses are blunted both at 8 AM and 11 PM (leading to reduced ΔΔTSH values) associated with normal peripheral thyroid activity [9]. Depressed patients with a past suicide attempt-and those who had no committed a suicide attempt within the past two years (i.e. patients with Suicidal Behavior Disorder [SBD] in early remission)-show no dysregulation of the HPT axis activity [10]. Depressed patients with current SBD (i.e. the suicide attempt occurred within the last year) are characterized by the co-occurrence of blunted evening TSH response to TRH-and consequently, markedly decreased ΔΔTSH values-and decreased circulating concentrations of FT4 (still within the normal reference range) and increased FT3/FT4 ratios [10]. In such patients, reduced responsiveness of the HPT system does not seem a consequence of the suicide attempt itself, but could be a preexisting state before the attempt, facilitating therefore the suicidal act. Moreover, violent suicide attempters show more severe HPT alterations than non-violent attempters [10].

Pathophysiological Applications

The decreased response of TRH-TSH, which reflects a decrease in pituitary TRH receptor functionality, may be the consequence of chronic hypothalamic TRH hypersecretion [11]. This hypothesis is based on the following data: 1) CSF TRH concentrations are elevated in depressed patients; 2) chronic administration of TRH inhibits nocturnal elevation of TSH in healthy subjects (and nocturnal secretion of TSH is blunted in depressed patients); 3) hypersecretion of TRH leads to a "down-regulation" (decrease in number) of pituitary TRH receptors. Another hypothesis is to consider the blunted TRH-TSH test response as a form of "subclinical hyperthyroidism". This can be argued by the fact that depression may be associated with a relative increase in T4 measurements (for review see [1]). However, given that TRH is able to directly stimulate the production of thyroid hormones at the peripheral level [12], the relative increase in T4 could also be of central origin. Indeed, there is a correlation between the decrease in TRH-TSH test response and the relative increase in circulating FT4 at both 8 AM and 11 PM [7].

A last hypothesis is to consider that the blunted test response to TRH is secondary to hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Indeed, it has been suggested that hypercortisolemia could induce decreased TRH mRNA levels in the mid-caudal paraventricular nucleus [13]. In agreement with several reports [5,911], but not all [1,13], it seems, however, unlikely that abnormal TRH drive could be secondary to hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis. In our previous studies [5,7,9,10] Post-Dexamethasone Suppression Test (DST) serum cortisol concentration and DST nonsuppression did not differ across the patients when classified according to their ΔΔTSH status.

From a pathophysiological viewpoint, the ΔΔTSH test takes into account 4 interdependent components of the HPT axis [14]:

- A chronobiological component-involving the determinants of circadian TSH secretion, (since ΔΔTSH is correlated with 24-hour TSH mesor and amplitude levels);
- A chronesthesic component-given that TRH receptor hyposensitivity (secondary to endogenous TRH hypersecretion) is more evidenced in the evening;
- A self-regulating component-The ΔΔTSH test takes into account the dynamic characteristics of the negative feedback of thyroid hormones on TSH secretion, since the morning TRH test stimulates secretion of thyroid hormones that may increase the negative feedback in the evening [7]. This could explain why, despite the expected circadian increase in TSH levels in the evening, basal TSH values do not change between 8 AM and 11 PM in healthy control subjects. In depressed patients, basal TSH values are lower at 11 PM than at 8 AM, and FT4 values are slightly but significantly higher at 11 PM, suggesting a strengthening of negative feedback by thyroid hormones at the pituitary level.
- A dynamic component-The evening TSH blunting in patients could also be related to a decrease in TSH resynthesis in the thyrotrophs during the day after the morning challenge, since TRH stimulates preformed TSH. This disturbance could involve a hyposensitivity of the TRH receptors (possibly because of prolonged TRH hypersecretion) and/or an increased negative feedback of thyroid hormones, both leading to under stimulation of TSH synthesis. On the other hand, especially in recent suicide attempters [10], a decreased central TRH activity-associated with reduced FT4 levels [10,15,16]-could also lead to such understimulation. Indeed, in a postmortem study Alkemade et al. [17] have found low TRH mRNA levels within the paraventricular nucleus suggesting a decreased hypothalamic TRH drive in depressed patients with persistent suicidal ideation.

Extensive evidence supports a role for TRH as a CNS homeostatic modulator: it has notably been implicated in the regulation of control circadian rhythmicity, arousal, seizure activity, autonomic function and spinal motor function [18,19]. According to the TRH hypothesis of depression [11], TRH hypersecretion may be seen as

a compensatory mechanism [20] in order to normalize serotonergic (5-HT) activity [21]. We postulated that a decrease in 5-HT function triggers an increased TRH secretion that secondarily normalizes 5-HT neurotransmission and also maintains normal thyroid hormone levels. Furthermore, we also suggested that this compensatory mechanism is not effective in depressed patients with a history of suicidal behavior [9,10]; this could play a role in the sustained 5-HT hypoactivity consistently linked to suicidal behavior (for review see [22]). Recently we have extensively discussed that central TRH function could be lowered in depressed patients with current suicidal behavior disorder, especially in violent attempters [10]. According to this hypothesis, the normalization of TRH function could reflect recovery from suicidality. This is further supported by the fact that HPT axis activity is normal in depressed patients with suicidal behavior disorder in early remission.

Therapeutic Applications

Prognostic significance in depressed patients

It is generally accepted that the presence of a positive (or abnormal) TRH-TSH test suggests the need for antidepressant somatic therapy. However, most studies have not established a link between the initial status of the HPT axis activity and the therapeutic response to antidepressants (for review see [23]). Thus, the initial status of the morning TRH test would have no predictive value (for review see 8). On the other hand, it has been observed that patients with the lowest pretreatment evening TSH secretion (basal and after 11 PM TRH stimulation) have the lowest rate of antidepressant response, and this may contribute to antidepressant treatment resistance [24]. In such patients, it has been speculated that adjunction of thyroid hormones, could be particularly beneficial to amplify antidepressant effects, since, by increasing the negative feedback on the hypothalamus, thyroid hormones may decrease TRH overproduction at this level.

Normalization of the HPT axis activity during antidepressant treatment is associated with a favorable clinical response. Thus, ΔTSH- and more obviously ΔΔTSH [24], is a "depressive state marker". The lack of normalization of the TRH test during recovery has a prognostic value since a blunted response would be predictive of a depressive relapse within 6 months [25]. In addition, normal ΔΔTSH values after 2 weeks of antidepressant treatment are associated with subsequent remission. Conversely, alteration of the HPT axis after 2 weeks of treatment is associated with drug resistance [8]. Normalization of the ΔΔTSH test suggests a restoration of a normal chronobiological activity of the HPT axis by antidepressants within the first two weeks of treatment. However, the mechanisms by which antidepressants could induce this change are poorly understood. Interestingly, administration of various antidepressant compounds may lead to decreased thyroid hormone levels by reduction of synthesis and/or metabolism, or enhanced clearance [26-28]. In clinical studies, greater reductions in T4 or FT4 levels have been consistently found in antidepressant responders compared to non-responders [29-32]. Thus, the decreased negative feedback may promote TSH resynthesis leading to adequate TSH reserves ensuring normal evening response in antidepressant responders.

On the other hand, it has been found that patients with a normal ΔΔTSH test at baseline were more often subsequent remitters [8]. Given that 1) the 5-HT tone is decreased when the HPT axis activity is normal in depressed patients, and 2) different types of antidepressant treatment enhance 5-HT neurotransmission, although each treatment achieves this result *via* different mechanisms [33,34], it is therefore conceivable that patients with a normal ΔΔTSH at baseline would better respond to antidepressant compounds.

Evolution of thyroid function during antidepressant treatment

Most studies found a decrease in thyroid function following chronic antidepressant treatment [29]. Tricyclic Antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs), but not Monoamine Oxidase Inhibitors (MAOIs), decrease serum T4 concentrations (without altering T3 and TSH levels). However, decreased thyroid function has been related to clinical recovery rather than to a direct effect of the antidepressant drug [24]. It is noteworthy that preclinical studies have shown that most antidepressants and mood stabilizers (e.g., desipramine, fluoxetine, lithium, carbamazepine, but not tranylcypromine [an MAOI]), significantly enhance type II 5' Deiodinase (D2) and inhibit type III 5 Deiodinase (D3), which catalyzes the inactivation of T3 to the biologically inactive 3,3'-diiodothyronine (3,3'-T2), increasing therefore T3 concentrations in different CNS areas [35,36]. These data strongly suggest that an increase in tissue concentrations of T3 may be a common effect of antidepressant or prophylactic treatment.

Preclinical studies have shown that acute Electro Convulsive Therapy (ECT), as well as Transcranial Magnetic Stimulation (rTMS), would have a direct effect on the HPT axis by 1) stimulating TRH and TSH secretions, and 2) decreasing T4 and T3 secretions [29]. In clinical studies, an increase in TSH secretion has been observed in ECT or rTMS responders, whereas changes in FT4 and FT3 were more inconsistent [37,38].

Total or partial sleep deprivation, both in depressed patients (uni- and bipolar) and in healthy controls, has been shown to induce a significant increase of the plasma values of TSH, T4 and T3 [39] (sleep inhibits the production of TSH). On the other hand, the TSH response to TRH after a night of sleep deprivation would be increased only in responder patients (that is, presenting the following morning a 30% reduction in their Sleep Deprivation Depression Rating Scale score).

Thyroid Hormone Treatment of Depression

Thyroid hormones can be used as adjuvant therapies. Although they have the ability to stimulate the activity of the catecholaminergic and serotoninergic systems, this explanation seems insufficient to account for the effectiveness of thyroid hormones in depression (for review see [14]).

Triiodothyronine (T3)

Owing to its rapid onset and offset of action-the half-life of T3 is approximately one day-T3 has been used in three ways to promote response to antidepressants:

- Acceleration studies (i.e., T3 is administered in addition to the antidepressant during the few weeks to shorten the time onset of antidepressant effects). Although coinitiation of T3 (20-62.5 μg/day) with TCAs, especially in women (for review see [40]), could accelerate the clinical response, coinitiation with SSRIs does not appear more

effective in reducing time response than SSRI monotherapy [41,42].

- Enhancement studies (i.e., T3 is administered in addition to the antidepressant throughout the length of treatment to enhance rates of antidepressant response). While coinitiation of T3 with SSRIs led to mixed findings, T3 doses of 20-62.5 µg/day initiated with TCAs led to significant clinical improvements compared to placebo (for review see [43]).

- Augmentation studies (i.e., T3 is added to current antidepressant monotherapy in patients who respond insufficiently). Numerous case series and open-label trials (for review see [44]) conducted in unipolar and bipolar depressed patients non-responders to treatment have suggested that the use of T3 potentiate the response to TCAs (approximately 50% of patients became responders within 2-3 weeks after the addition of 20-50 µg of T3). However, the data of 8 controlled double-blind studies are only partially supportive of the results given in the open studies [45]. The data on the use of T3 augmentation with newer classes of antidepressants (SSRI, SNRI [serotonin noradrenaline reuptake inhibitor], bupropion, mirtazapine) appears less clear than for the TCAs [46]. Overall studies evaluating T3 supplementation in depressed patients show that it is well tolerated [47].

Thyroxine

There are few methodologically reliable studies that have assessed the effects of T4 in treatment-resistant depression. Owing to its long half-life (6-7 days)-leading a steady state needs at least three to four weeks after the last increase-T4 does not appear suitable to accelerate the response to antidepressants. Therefore, T4 has been used in two ways in the treatment of mood disorders:

- To improve treatment response in patients who are not responsive to antidepressant trial (augmentation studies). Moderate (100 µg/day) to high dose of up to 600 µg/day of T4 seems effective in euthyroid unipolar and bipolar refractory depressed patients (for review see [40,48]). T4 administration was well tolerated in most studies. Some studies suggest that T4 supplementation would be more beneficial in bipolar depressed women than in men [49].

- As a mood stabilizer for rapid cycling bipolar patients (maintenance studies). Supraphysiological T4 doses (i.e., > 200 µg/day) in addition to mood stabilizers may improve the course of patients with bipolar disorder preventing affective episodes in approximately 60% patients, and decreasing the number of recurrences and hospitalizations (for review see [50]).

However, distinguishing the T4 and T3 in the treatment of refractory bipolar depressed patients, or rapid cycling bipolar disorder, does not appear really valid at present. Moreover, before generalizing the use of thyroid hormones as adjunctive therapy, additional data on tolerability and long-term safety are needed.

Thyrotropin-Releasing Hormone (TRH)

Administration of TRH in the morning at a dose of 500 µg parentally showed rapid antidepressant effects, albeit transient, in depressed women [51]. However, these preliminary findings were not replicated, including controlled double-blind studies using doses up to 1000 µg Iv [52]. Nocturnal TRH administration (500 µg Iv) at midnight induced a ≥ 50% reduction in baseline total score of the Hamilton Depression Rating Scale (HDRS) within 24 hours in 6 of 10 bipolar depressed patients (60%); the antidepressant response continued up to 2 weeks in most patients who were subsequently treated with antidepressant drug therapy [53]. However, TRH has minimal blood-brain barrier penetration because of highly hydrophilic nature, and is rapidly degraded in the periphery (serum half-life is about 3-5 minutes). Thus, intrathecal TRH infusion (500 µg), *via* lumbar puncture, has been administered in refractory depressed patients leading to a rapid antidepressant response (≥ 50% reduction in HDRS scores in 5 of 8 drug-free pat ents) [54].

Stable TRH analogs and prodrugs, with reduced affinity for TRH-R1 receptors (responsible for endocrine activity), are in preclinical or clinical development in order to increase the duration of action and decrease degradation [55]. Finally, direct nose-to-brain delivery of TRH in sustained-release biodegradable nanoparticles is a promising mode of therapy [56], in particular for suicide prevention (for review see [57]) where TRH function is supposed to be lowered.

Conclusion

In all depressed patients, thyroid function should be assessed in order to detect frank or subclinical dysthyroidism. Altered HPT functioning may lead to pharmaco-resistance and therefore should be corrected. Nevertheless, most depressed patients are euthyroid, while showing subtle chronobiological alterations-these alterations are only evidenced with specific approaches such as the ΔΔTSH test.

Depending of the clinical context, central TRH secretion might be increased, decreased or normal, independently of the HPA axis activity. In the frame of the "homeostatic hypothesis of depression", TRH may be seen as a compensatory mechanism in order to normalize 5-HT activity. In this case the initial 5-HT deficiency leads to an increase in TRH activity which secondary normalizes 5-HT activity. When, for unknown reasons, this mechanism is not effective, as observed in suicide attempters, 5-HT activity remains reduced. However, normal TRH activity, as observed in SBDs in early remission, might prevent a new suicide attempt despite low 5-HT tone. On the other hand, it is also suggested that the co-occurrence of decreased 5-HT tone and decreased TRH activity may precipitate a suicide attempt. Therefore, decreased hypothalamic TRH activity may play key role in the pathogenesis of suicidal behavior. Future studies are needed to confirm the potential anti-suicidal properties of TRH.

Changes in thyroid function that may occur during antidepressant medication appear related to clinical recovery rather than to a direct effect of the antidepressant drug. Moreover, chronobiological restoration of the HPT axis activity may precede clinical remission. It has been hypothesized that antidepressant could normalize thyroid function by enhancing T4 to T3 conversion in the brain as well as by direct effects on the hypothalamic TRH neurons [1].

Finally, there is good evidence to suggest that thyroid hormone administration is helpful in the treatment of mood disorders, but limited data are available on long-term safety. However, the current state of knowledge does not predict which patients with unipolar or bipolar depression are likely to respond to thyroid augmentation strategies. Further evidence will help settle the questions regarding utility of thyroid hormone in management of euthyroid unipolar and

bipolar depression, including optimum dose, duration of therapy, long-term safety, and effectiveness of this approach.

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