review article _____

The relation between thyroid function and depression: a review

A relação entre a função tireoidiana e a depressão: uma revisão

Saint-Clair Bahls[a] and Gisah Amaral de Carvalho[b]

[a]Department of Psychology of the Federal University of Paraná (UFPR). Curitiba, PR, Brazil. [b]Department of Medical Clinic of the UFPR. Curitiba, PR, Brazil

Abstract

Objective: The role of the thyroid gland in primary depressive disorder is unclear. Although there is evidence that patients with subtle underlying defects in thyroid function may be more prone to developing depressive disease, the specific abnormality in thyroid function associated with depressive disorders remains poorly understood. In this review, we outline the major findings concerning depression and thyroid function, with particular attention on the relationship between thyroid function and cerebral monoamines.

Methods: Literature searches were performed by Medline, with secondary-source follow-up.

Results: The documented hypothalamus-pituitary-thyroid (HPT) axis abnormalities in some depressed patients are: elevated T_4 concentrations, abnormal TSH responses to TRH; presence of antithyroid antibodies and elevated CSF - TRH concentrations. The relation of these abnormalities of HPT function, the main monoamines and the diagnostic subtypes of patients with depression is complex and does not directly support a linear relationship.

Conclusions: After many years of research, the precise relationship between the HPT axis and depressive disorders remains obscure, and the mechanism underlying the thyroid abnormalities in depressive patients remains indeterminate. Thus, considerable further investigation will be necessary to understand the role of the HPT axis in the pathogenesis and treatment of depressive disorders.

Keywords

Thyroid function. Depressive disorders. Cerebral monoamines.

Resumo

Objetivo: O papel da função tireoidiana nas doenças depressivas é pouco claro. Embora existam algumas evidências de que discretas alterações tireoidianas predisponham a casos de depressão, as anormalidades específicas envolvendo a tireóide e os quadros depressivos permanecem pouco conhecidas. Serão destacados nesta revisão os principais achados envolvendo os quadros depressivos e a função tireoidiana, com especial atenção na participação das monoaminas cerebrais nesta relação.

Método: Foram realizados levantamento no sistema Medline e na literatura.

Resultados: Existem evidências de atividade alterada do eixo hipotálamo-hipófise-tireóide (HHT) em alguns casos de depressão, que incluem: aumento dos níveis de T_4, resposta alterada do TSH pós-estímulo com TRH, presença de anticorpos antitireoidianos e concentração elevada de TRH no LCR. A relação entre estas anormalidades, as principais monoaminas cerebrais e os subtipos de quadros depressivos é complexa e ainda não permite o estabelecimento de hipóteses diretas de compreensão.

Conclusões: Após anos de pesquisas, permanece pouco esclarecida a importância da relação entre o eixo HHT e as depressões, assim como os mecanismos subjacentes às alterações tireoidianas encontradas nos pacientes deprimidos. Portanto, mais pesquisas serão necessárias para uma melhor compreensão do papel do eixo HHT na patogênese e no tratamento dos quadros depressivos.

Descritores

Função tireoidiana. Transtornos depressivos. Monoaminas cerebrais.

Introduction

The relationship between and the interest in the brain and the thyroid function was established long time ago. According to Esposito et al,[1] this connection was first recorded by Parry in 1786. Only approximately one century after that, in 1873, Gull demonstrated the association between myxedema and psychosis. The Committee of the Clinical Society of London confirmed this relation in 1888 reporting that 36% of the patients with myxedema also had insanity symptoms. In 1949, Asher described the association between hypothyroidism and insanity in 14 clinical cases, named 'myxedema madness' and pioneerly warned that a melancholic state, in the presence of hypothyroidism, would be reverted with the corrective utilization of thyroid hormones (TH). This observation encouraged clinicians to experience the efficacy of these hormones in the treatment of depression.[2]

Afterwards, it was demonstrated that thyroid hormones are essential for the normal development and functioning of the brain, being absolutely necessary, especially thyroxine (T_4), for the maturation of the fetal brain. In 1999, Haddow et al[3] demonstrated that maternal deficiency of TH during pregnancy leads to a delay in the neuropsychomotor development of children. TH regulate the neuronal cytoarchitecture, the normal neuronal growth and the synaptogenesis, and their receptors are widely distributed in the central nervous system.[1,4]

In patients with endocrine diseases there has been commonly found a high prevalence of mood disorders in general and particularly of major depression (MD), a fact that originated psychoneuroendocrinology.[1] Specifically regarding thyroid diseases, according to the review by Boswell et al,[5] the prevalence of depressive symptoms in hypothyroidism is near to 50% whereas in hyperthyroidism it reaches up to 28% of the cases. Clinical depression occurs in more than 40% of people suffering from hypothyroidism.[6] In psychiatric populations,[7] the rate of clinical hypothyroidism ranges from 0.5 to 8%. As to patients primarily diagnosed with MD, there is rarely a picture of overt hypothyroidism, although in cases of refractory depression the rate of this thyroid dysfunction[8] reaches more than 50%.

The link between mood disorders and abnormalities of the hypothalamus-pituitary-thyroid (HPT) axis can be studied in three ways: 1) by the assessment of functional thyroid tests in patients with primary mood disorder 2) by the effect of antidepressive treatments in the functional thyroid tests and 3) by the use of thyroid hormones in the treatment of primary mood disorder. In this review we will comment on the first item of this association, reporting the abnormalities of the HPT axis in patients with major depression and we will try to examine these alterations relating them to brain monoamines. For that, we used Medline and secondary-source search.

Depression and the hypothalamus-pituitary-thyroid axis

Thyroxine (T_4)

Total and free plasmatic T_4 has been found as normal or increased in depressed patients, and nearly 20% to 30% of them have levels above the normal limit. Even within the normal range, T_4 rates tend to decrease as soon as depression is remitted.[2,9] Esposito et al[1] postulate that high T_4 levels are a favorable indicator of antidepressive response.

One research[10] has found a correlation between the severity of depression and increased levels of T_4 and Kirkegaard and Faber[11] have warned that although a possible explanation for the malnutrition state which occurs in profound depression (and which may lead to alterations in the HPT axis, with high plasmatic levels of T_4 and 3,3',5'-triiodothyronine (rT_3) and decreased levels of triiodothyronine (T_3), this condition would be only applied to some cases of severe depression. In a turnover study with depressed subjects it was found a significantly high rate of daily production of T_4 in 30% of patients,[12] suggesting that thyroid is abnormally stimulated in depression.

Depressed patients refractory to tricyclic antidepressants (TAD) respond better to augmentation with thyroid hormones when they present low normal T_4 serum levels than patients with medium and high normal serum levels.[2]

We found that the concentration of free T_4 in the cerebrospinal fluid (CSF) was relatively increased during depression, being reduced when the clinical recovery occurs.[13] This leads to the idea that depression is associated with a relative hyperthyroidism state and that the decrease of brain T_4 is needed for an adequate antidepressive response. Authors suggest that the level of T_4 in the CSF follows the serum level.

One explanatory hypothesis for the mechanism of T_4 increase in depression is based on the increase of cortisol (hypercortisolism of depression), believed to lead to an activation of the hypothalamic neurons which produce the thyrotrophin releasing hormone (TRH) and, consequently, of the thyroid function. Bruhn et al.[14] found that the exposition of glucocorticoids in hypothalamic cultured fetal rats increased the genic expression of TRH. Hypercortisolism of depression probably occurs due to an impaired functioning of the hypocampus, which is the negative feedback site of glucocorticoids along the hypothalamic-hypophyseal-adrenal axis.[2] Therefore, the existence of a functional disconnection between the hypothalamus and other brain areas can remove the inhibitory influence of the hypocampus in some depressive pictures, favoring hypercortisolism and consequently the increase of T_4.

Contrarily to most authors, Bauer and Whybrow[15] propose that in some cases of depression the brain would be TH-deficient and the relative increase of thyroxine would exert a compensatory role in the maintenance of the 'affective homeostasis', offering more T_4 for the brain with deficiency of this hormone, seeking therefore to normalize its function.

It is important to highlight that transient T_4 elevations were found in patients recently hospitalized with clinical or psychiatric pictures, with spontaneous normalization within a two-week period.[9] The decrease in the thyroid levels after treatment may be caused by a non-specific stress-decreasing effect which occurs with the improvement of the depressive picture.

Triiodothyronine (T_3)

T_3 serum levels in depressed patients are frequently normal, but in two studies reduced levels were identified, typically in

more severe conditions.[10,16] However, we must take into account that innumerable factors influence T_3 plasmatic levels such as: hunger, malnutrition, concomitant clinical diseases and the use of medications. All these factors tend to decrease[11] the peripheral levels of T_3, hampering the interpretation of the results found in research. Using ultra-filtering, the most employed laboratory measuring method, Kirkegaard & Faber[17] have not found alterations in the free T_3 serum levels in depressed patients.

In one study, the daily production of T_3 among non-medicated and moderately depressed subjects was within the normality,[12] raising the hypothesis that the combination of the production of increased T_4 with the production of normal T_3 suggests a conversion by deiodination of T_4 into reduced T_3 during depression. This phenomenon can be caused by the reduction in the enzymatic activity of deiodination, although the site where this may occur is not known. Theoretically it may be in the brain, but there is no information about intrabrain T_3 or of T_3 CSF levels in depressed subjects.[11]

As to the use of T_3 as an adjuvant in the treatment of depression, it is proposed that T_3 corrects a brain abnormality of thyroid hormones considered as an important patophysiological component of depression. But, due to the fact that the brain self-regulates the transformation of T_4 into T_3, plasmatic rates are not always representative of the central thyroid activity.[9]

As there is evidence that T_3 primary brain action occurs via intracellular receptors which, subsequently, influence the genic expression,[4] it is regrettable the absence of studies about brain T_3. Even studies concerning its peripheral level, do not provide conclusive evidence, although the literature has an almost complete acceptation that there are no significant plasmatic alterations of T_3 in depressive disorders.

3.3'.5'-triiodothyronine (rT₃)

rT_3 or reverse T_3 is the inactive analogous of T_3. The first study that has evaluated rT_3 plasmatic levels in unipolar depressed patients of both genders found high serum levels of this hormone.[18] Afterwards, the same group also found high rT_3 plasmatic levels in female patients with manic pictures.[19] In 1981, Kirkegaard & Faber[16] confirmed the findings of the first study and also investigated patients with unipolar depression. In other study these findings were not confirmed.[20] Therefore, the alterations found in rT_3 free and total plasmatic levels in depression, when they occur, use to accompany the alteration of thyroxine, but perhaps are not specific.

It has been proposed that depression causes an inhibition in the 5'-deiodinase type II (D-II) enzyme, probably due to the increase in cortisol levels.[21] This enzyme is responsible for the transformation of T_4 into T_3 in the brain, and, consequently, its inhibition triggers the conversion of T_4 by other enzyme, type III brain 5'-deiodinase (D-III), therefore producing rT_3. Thus, in depression one should expect an increase in the CSF and plasmatic levels of rT_3 which is, in turn, a potent inhibitor[4] of the D-II enzyme, what may favor even further its production in the brain. A defect in the brain deiodinases can be a pathogenic factor in depression.

In 1983, Linnoila et al[22] investigated the CSF level of rT_3 in five different populations of patients with affective disorders (endogenous unipolar major depression, non-endogenous unipolar major depression; type I bipolar disorder manic episode, type I bipolar disorder depressive episode and type II bipolar disorder depressive episode). Significantly higher levels of rT_3 in the CSF were found in endogenous unipolar depression compared to other affective conditions. The authors suggest that rT_3 alterations are peripherally found both in unipolar depressive conditions and manic conditions, whereas central alterations only occur in endogenous unipolar depressive conditions. The possible reasons for this difference were not examined, but they raised the hypothesis that, in endogenous depression, being T_4 transformed in the brain into rT_3 (inactive) rather than into T_3 (active), there is a relative central hypothyroidism condition. Nevertheless, the proportion of free rT_3 in the CSF of depressed subjects is approximately 26-fold the plasmatic concentration,[13] without change after clinical recovery, suggesting that intrabrain concentration of rT_3 is normally high in human beings, probably not representing a pathogenic factor for depression,[11] questioning the hypothesis of central hypothyroidism.

Thyrotropin (TSH)

The dosage of plasmatic TSH is the most recommended test to assess the thyroid function, and the normal range of variation in the general population,[23] for most laboratories, is situated between 0.35 and 5.50 mIU/L.

Some studies with depressed patients found a reduced basal serum level of TSH, but within the normal variation range.[24] However, one study comparing endogenous depressed patients with patients with hypothyroidism who were receiving reposition with thyroxine[12] found significantly higher plasmatic levels of TSH among depressed patients (0.90 x 0.11 mU/l), suggesting an inappropriate secretion of TSH (in relation with the high production of T4) in endogenous depression, compatible with some degree of central thyroid overstimulation in non-treated depressed patients. However, these findings may only indicate that patients with hypothyroidism were receiving high doses of hormonal reposition. Cleare et al[25] found a positive relation between depressive scores and the increase in TSH levels, confirming previous findings of this same group.[6]

A probable hypothesis for the increase in serum TSH in depression stems from the observations that the plasmatic level of this hormone is also influenced by somatostatin, which inhibits its release by the hypophysis. Some studies found a reduction in somatostatin in the CSF of depressed subjects,[26,27] and this may contribute for the increase of serum TSH in depressive conditions.

TSH plasmatic levels in depressed patients, as observed by the cited studies, were not conclusive, but the circadian variation of serum TSH in healthy subjects is associated with an increase near to midnight (between 22 p.m. and 4 a.m.), which in cases of non-treated depressions seems to be attenuated or absent.[28] A study by Bartalena et al[29] assessing women with non-treated endogenous MD and a control group has not found differences in the matutinal serum levels of TSH, whereas noc-

turnal values were significantly lower among depressed subjects, with the night peak being abolished in 14 out of the 15 depressed women. Out of nine depressed patients with normal values of matutinal TSH, the night peak was abolished in eight, although the response to the TRH test was normal in the whole group; the authors concluded that endogenous MD is associated with an important impairment in the nocturnal secretion of TSH, being a more sensitive alteration of the HPT axis in endogenous depression than the TRH challenge test.

After the complete recovery from depression this nocturnal variation of TSH is reestablished, but in cases in which the recovery from depression does not occur or is incomplete this variation of TSH remains attenuated or absent. Partial sleep deprivation,[30] which has an antidepressive effect, leads to the reestablishment of the nocturnal increase of TSH with the consequent increase in T_3 and T_4 serum levels. Therefore, this nocturnal reduction in TSH can lead to a global decrease in the secretion of thyroid hormones, enabling a certain degree of central hypothyroidism in some depressed patients.[2,29]

Response of TSH to TRH

The response of the TSH test to TRH intravenous stimulation has been assessed as the peak value minus the basal value, called as delta-TSH (ΔTSH).

In 1972, Prange et al,[31] in patients with MD, observed the presence of 25% of cases with a decreased response of TSH to TRH stimulation, and all these patients presented TSH, T_3 and T_4 normal plasmatic levels. Still in that year Kastin et al[32] confirmed those data, afterwards reconfirmed by other studies which defined this decreased TSH response to TRH as the most widely recognized evidence of thyroid axis abnormality in depression. This decrease or 'blunted' response to TSH occurs in 25 to 30% of depressive conditions. Endogenous conditions are those which present the lowest levels of basal TSH and of ΔTSH, with approximately 25% of endogenous depressions having a ΔTSH below 2 mIU/L.[21,23,33]

In the classical review by Loosen & Prange,[33] of 45 studies with the TRH challenge test in depressed subjects, 41 articles (n=917) confirmed that nearly 25% of the cases had a decreased response and the other four studies which had not confirmed such a response examined a total of twenty patients. Nevertheless, Shelton et al[34] have recently found only 3% of decreased response in a group of ambulatory patients with major depression. Other study[35] found 16% of decreased responses among ambulatory depressed patients, what was not statistically different from the control group. It should be highlighted that in these two studies the depressive conditions were not restricted to the endogenous subtype. It is also hypothesized that higher rates of decreased response to the TRH test occur in hospitalized depressed patients.[34]

It is important to highlight that the decrease of TSH response to TRH is also found in other conditions such as alcoholism, panic disorder and elderly men.[1,5,36]

The clinical recovery from the depressive condition uses to normalize this altered response and some authors have demonstrated that patients with endogenous depression who have early

relapses have not normalized the decreased TSH response to TRH.[37,38] Therefore, the maintenance of the dysfunction in the HPT axis, independently from the clinical improvement, suggests that patients are not totally recovered. These authors propose that the normalization of ΔTSH predicts clinical recovery. However, two studies with antidepressants have not confirmed these findings related to the predictive value of the TRH test.[10,38] Therefore, there is still no consensus about the possibility of a decreased TSH response to TRH representing a trait or state condition in endogenous depressed patients.[21] Kirkegaard & Faber[11] warned about the possibility that the use of antidepressants interfere with the HPT axis in multiple sites, hampering the interpretation of these results.

On the other hand, there are studies with depressed patients which found an increased TSH response to TRH.[39,40] It is calculated that nearly 10 to 17% of depressed subjects showed an exaggerated response to the test.[21,41] These cases use to have normal TSH, T_3 and T_4 plasmatic levels, the so-called 'grade III hypothyroidism'. In 1982, Gold et al[42] found 60% of cases with positive antithyroid antibodies among depressed patients with exaggerated response to TRH, being the first report that some depressive pictures show high rates of asymptomatic autoimmune thyroiditis.

Recently, Kraus et al[23] have investigated 60 depressed patients (not only melancholic, ambulatory and hospitalized ones) with stables doses of psychopharmacological medication and TH, and TSH serum levels in the superior half of the normal variation range (3.0 to 5.5 mIU/L). They found 38% of them with an excessive response to the TRH test, significantly higher than in the general population (6%), with a gender distribution of 43% among females and 23 % among males. When subpopulations of the sample were assessed - only ambulatory patients and only patients without hormonal reposition therapy -, there were still 38% of exaggerated responses. They concluded warning about the probability that mild alterations in the thyroid function may contribute for depression in some cases, and that special attention should be given to patients with normal serum TSH levels between 3.0 and 5.5 mIU/L, suggesting the utilization of the TRH challenge test as the most sensitive one to investigate the thyroid alterations which could contribute to the depressive picture and/or hamper their recovery.

Bipolar depressions and TAD-resistant pictures show a slight basal increase of serum TSH (nearly 20% with levels above the normal superior limit), or an exaggerated response of TSH to TRH stimulation. Targum et al[41] have investigated patients with refractory depression and found that 29% of them had an exaggerated response to the TRH test and Gitlin et al[43] found a rate of 31% in cases of refractory depression, probably reflecting a certain degree of thyroid insufficiency.[11]

Subclinical hypothyroidism

The development of measures to assess TSH at the beginning of the '70s allowed the understanding of the picture of subclinical hypothyroidism, recently called minimal thyroid insufficiency (MTI). MTI is a common condition, being defined in laboratory as a high basal concentration of TSH in the

presence of normal T_3 and T_4 plasmatic levels. MTI is a mild form of hypothyroidism with discrete somatic manifestations of thyroid deficiency. In some cases, there can be typically depressive symptoms, mainly: mental lentification, discouragement, lethargy and apathy. It uses to be present some years before the appearance of an overt hypothyroidism picture and it is proposed that depressive symptoms in the presence of TMI use to respond inappropriately or partially to antidepressive therapy.[9,23]

Depressive pictures use to show high rates of minimal thyroid insufficiency.[8] Haggerty & Prange[44] reported that 15 to 20% of depressed patients show TMI and can have poorer responses to antidepressive therapies. In cases of refractory depression these rates are even higher. Howland,[8] in his review of six studies, found a mean rate of 52%, contrasting with that of 8 to 17% in depressed patients in general, and concluded that TMI is significantly associated with refractory depressive pictures.

Patients with TMI have higher prevalence of depression than the general population and it has been proposed that minimal thyroid insufficiency shares with overt hypothyroidism the capability of causing depression,[1] being considered one of the main risk factors in non-elderly women, with 56% prevalence in lifetime for MD in this population as compared to 20% in the euthyroid population.[45]

Thyrotropin-releasing hormone (TRH)

Studies on TRH are scarce and inconsistent in depressed patients. Some studies,[46,47] in non-medicated depressed patients, found high levels of TRH in the CSF, although other study found normal levels.[48]

Banki et al[47] assessed brain TRH among depressive and manic pictures and among controls, all of them non-medicated. Depressed patients showed an increase in TRH levels nearly threefold than controls. This chronic stimulation of TRH in the hypophysis could be responsible for the TSH and T_4 serum alterations found in depressed patients. Other study found that the repeated administration of TRH causes a blunted response to the TRH challenge test, such as in depressive pictures.[49]

It is suggested that in some depressive pictures the stimulation of thyrotrophs (hypothalamic TRH neurons) occurs due to an increase of glucocorticoids leading to a TRH-increased secretion. This chronic hypersecretion would cause the adaptive phenomenon of down-regulation of hypophyseal-TRH receptors, resulting in the 'blunted' response of TSH to exogenous TRH.[2,21,28]

Antithyroid antibodies

The presence of antithyroid antibodies (antimicrosomal and antithyreoglobulin) defines the autoimmune thyroiditis condition, Hashimoto being the most common thyroiditis, responsible for important part of hypothyroidism pictures.

Autoimmune thyroiditis is found in nearly 15% of depressed patients with exaggerated response to the TRH stimulation test. Nine to twenty percent of hospitalized patients who complain predominantly about depression are positive for antithyroid antibodies.[42,50] Some authors[21,42] suggest that in patients who complain about depression and apathy the presence of antythyroid antibodies should be always assessed.

In the study by Nemeroff et al[50] with hospitalized patients, MD pictures were those with the highest rates of antythyroid antibodies. As a rule, normal levels of thyroid hormones, accompany the positivity for these antibodies, configuring asymptomatic autoimmune thyroiditis. In this study there was a predominance of females, what could have contributed to this result, as women show antythyroid antibodies rates three- to five-fold than that of men.[9]

In rapid cycling bipolar cases[11,21] the prevalence of autoimmune thyroiditis reaches 50%.

Depressed patients seem to have a higher prevalence of autoimmune thyroiditis compared to the normal population. These findings agree with the idea that mild alterations of the thyroid function mimic depression or increase the vulnerability for affective disorders.

Blood-brain barrier and TH transportation

Transthyretin (TTR) is one of the T_4 serum-transporting proteins representing 10 to 25% of CSF proteins.[51] The affinity of T_4 for TTR is 39.3%, compared to only 1.4% for T_3, demonstrating a certain specificity in the transportation of T4 into the brain.[52] Only one study has investigated this protein in depressive disorders and has found levels significantly decreased of TTR among patients with refractory major depression as compared to the control group, and the authors have suggested that the low levels of this transporting protein may cause 'brain hypothyroidism', accompanied by peripheral concentrations of thyroid hormones within the normal range.[51] With the lower availability of thyroid hormones in the brain there is an increase in the hypothalamic production of TRH, resulting in increased values of TRH in the CSF and a in decreased response of TSH to TRH. The authors[51] suggest that a thyroid dysfunction may represent a pathophysiological phenomenon in a subgroup of depressed patients.

Relationship between alterations of the hypothalamus-pituitary-thyroid (HPT) axis and brain monoamines

Serotonin (5-HT)

Evidence that serotonin, a neurotransmitter strongly involved in depressive states,[53] also has a pathophysiological role in thyroid diseases stems from several observations. Brain serotonin synthesis and turnover in rats is decreased in hypothyroidism[54] and increased in hyperthyroidism.[55] In animals with hypothyroidism it was found a decrease in the sensitivity of serotonin receptors[56] and a compensatory increase in the density of $5HT_{1A}$ receptors, secondary to the reduction in the levels of synaptic serotonin.[57]

In human beings, serotonin plasmatic levels are positively correlated to T_3 concentrations, being increased in hyperthyroidism, and with the decrease in the thyroid hormones due to antithyroid treatment, serotonin serum levels use to be reduced.[6]

In the investigation of the interaction between the thyroid

function and the serotoninergic system it was found a significantly decreased cortisol and prolactine response to the 5-HT d-fenfluramine agonist among patients with non-treated hypothyroidism, suggesting a decreased 5-HT central function in these cases.[6] This same group of researchers,[25] in a further investigation on the serotoninergic function in patients with hypothyroidism, have confirmed the previous findings and noticed that the serotoninergic function was normalized by reposition therapy with thyroid hormones. They have concluded that their data reinforce the possibility that brain serotoninergic neurotransmission is decreased in hypothyroidism and suggest that this reduction of 5-HT responsiveness is reverted with thyroid hormonal reposition.

A probable reason why thyroid hormones interact with serotonin stems from the observation of the effect of these hormones on the serotoninergic auto-receptors. The administration of thyroid hormones on animals with induced hypothyroidism and also on euthyroid animals has caused an increase in the cortical serotonin and a desensitivization of the $5HT_{1A}$ inhibitory self-receptors in the raphe.[58] This functional decrease of self-receptors results in an increase in the cortical and hyppocampal 5-HT release.[58] These findings were confirmed in a recent *in vivo* study,[59] with euthyroid rats, which reported a significant decrease in the self-inhibitory sensitivity of the $5HT_{1A}$ receptor induced by administration of T_3. These results indicate[60] that the use of T_3 can reduce the activity of the $5HT_{1A}$ self-inhibitory receptors and, then, increase the cortical release of 5-HT.

Other source of evidence for the interaction of serotonin with thyroid alterations originates from studies with enzymes which metabolize the thyroid hormones. As seen before, intrabrain T_3 is mainly the result of local production through deiodination of T_4 by type II deiodinase enzyme. D-II enzymatic activity is increased in hypothyroidism and decreased in hyperthyroidism and type III deiodinase, contrastingly to D-II, has its activity increased in hyperthyroidism and decreased in hypothyroidism.[11] D-II activity increases the production of T_3 in the brain and hypophysis, and consequently also the local production of serotonin. It is supposed that D-III activity decreases the local concentration of T_3 and, indirectly, brain serotonin.[11] It is observed that both in hypothyroidism and hyperthyroidism the functioning of these thyroid-hormone metabolizing enzymes can affect the brain levels of serotonin.

On the other hand, it has been suggested[21] that depression causes an inhibition of type II deiodinase enzyme leading to a decrease in the brain levels of T_3 and, consequently, also contributing to the decrease of serotonin in depressive pictures. The use of desipramine[61] and fluoxetine[62] in rats showed an increase in the activity of D-II, and fluoxetine[62] also decreased the activity of D-III. As a consequence an increase of brain T_3 and 5HT should occur, offering one more source to regularize the neurotransmitter in cases of depression.

Other way of analyzing the alterations of thyroid hormones found in cases of depression stems from the observation that TRH seems to undergo a constant inhibition due to the presence of serotonin,[63] and if there is a decrease in brain serotonin levels it would occur an increase in brain TRH, which can, consequently, stimulate the secretion of TSH. The increase of TSH would produce an increase in the production of T_3 and T_4, tending to reduce the serum level of TSH through feedback, reaching a new state of plasmatic equilibrium which would be situated within the normal variation range. This 'new' level of TSH is inappropriately high in relation[12] to the increased production of T_4.

The hypothesis of serotonin deficiency can explain the low Δmax TSH found in depression and the reason why patients with persistently low Δmax TSH after apparent recovery from depression were subjected to early relapses.[36,37] Low Δmax TSH has been proposed as a marker of active depressive disorder. Kirkegaard & Faber[11] believe that serotonin deficiency is, at the same time, a main pathogenic factor in depression and also sufficient to explain the alterations in the HPT axis in depressed patients, especially endogenous ones. This statement seems to us somewhat premature as the study of the HPT axis and depressive pictures show some evidence of the pathophysiological action of serotonin, but can not be taken as conclusive as there are still controversial and uncertain points due to the high complexity of the psychoneuroendocrinological relationship in this area, which just starts being analyzed. For example, comorbidity of depression and hyperthyroidism does not sustain the hypothesis of serotoninergic deficiency with the existent evidence in the literature.

Further neuroendocrine studies are needed to assess subtypes of 5-HT receptors aiming to confirm and explain more specifically the pathophysiological condition of serotonin in thyroid alterations.

Catecholamines

Other widely-accepted etiological hypothesis of depression is the deficiency of catecholamines, especially noradrenalin (NE) ,[53] and there is some evidence associating this monoamine and the HPT axis.

Immunohystochemical experimental studies in animal brains showed that T_3 has a high concentration in sinaptosomes,[64] especially those located in noradrenergic neurotransmission brain nuclei.[65] Afterwards, Rozanov & Dratman[66] confirmed the previous findings and found increased T_3 concentrations in the locus coeruleus and in the lateral tegmental nucleus of rat brains. These studies suggest that T_3 has some special function in these noradrenergic nuclei and some authors consider that T_3 can exert a neuromodulating or neurotransmitting role in the central noradrenergic system.[60]

The availability of noradrenalin is essential for the transformation of T_4 into brain T_3.[67] In a recent study, Gordon et al,[68] besides reconfirming that T_3 is concentrated in the noradrenergic neurotransmission sites, have situated the main site of processing and distribution of this hormone in the locus coeruleus. Such a distribution is performed anterogradely, reaching the noradrenergically innerved superior brain structures and the authors concluded highlighting that T_3 functions as a cotransmitter of brain noradrenalin.

As early as in 1969, Prange et al[69] proposed that T_3 caused an

increase in the sensitivity of the brain noradrenergic receptors. T_3 acts, therefore, on the noradrenergic neurotransmission system and augments its effects probably increasing the activity of the post-synaptic beta-adrenergic receptors.[70] This action is similar to that provided by the celebrated antidepressive agents, what can explain the reason why T_3 is efficient to maximize antidepressive therapies, even in euthyroid patients. In 1981, Whybrow & Prange[70] hypothesized that thyroid hormones accelerate the recovery from depression, as they increase the function of the beta-adrenergic receptors. In that same year, Morley[63] identified that noradrenalin participates in the stimulation to the release of TRH and TSH. The decrease in the thyroid activity may result in the decrease in the activity of the beta-adrenergic post-synaptic receptors, causing a functional decrease in the noradrenergic neurotransmission.[9]

Adrenergic alterations occur in thyroid diseases, and it was found an increased number of beta-adrenergic receptors in the lymphocytes of animals and patients with hyperthyroidism, contrarily to what happens in hypothyroidism.[71,72] In the review by Henley and Kohenle[4] it is mentioned that in rat brains there is a slight decrease in the cortical density of beta, alfa$_1$ and alfa$_2$ receptors in hypothyroidism and an increase in hyperthyroidism.

Linnoila et al,[22] discussing the hypothesis of central hypothyroidism in endogenous depressive pictures, which would be caused by the transformation of T_4 into brain rT_3, suggest that the deficiency of T_3 in the brain can alter the noradrenergic neurotransmission, probably through an inversion between the adrenergic receptors, with the predominance of alpha- over beta-adrenergic ones. Other studies with animals have found a reduction in the beta-adrenergic receptors in hypothyroidism pictures, suggesting that TH can stimulate these receptors.[73] Healy et al,[74] assessing depressed patients, found a significant decrease in the beta-adrenergic receptors in the responders after six weeks of antidepressant therapy.

Animal models of refractory depression[8] strongly suggested the participation of thyroid alterations, especially hypothyroidism, probably mediated by the alteration in the beta-adrenergic function. Howland[8] states in his review that studies with animals vigorously support the implication of the beta-adrenergic neurotransmission system in the pathogenesis of refractory depression associated with hypothyroidism.

There is still the need of replicating these findings in systematic studies and noradrenalin deficiency still cannot explain some alterations in the HPT axis found in depression, especially the increase of TRH in the CSF. However, this hypothesis is compatible with the benefic effect of T_3 in the treatment of some cases of depression.

Conclusions

Although most depressed subjects have normal T_3, T_4 and TSH circulating levels, there is evidence of altered activity of the HPT axis in some cases of depression including; 1) increase in the total and/or free T_4, many times within the normality levels. It is characteristic the finding of high plasmatic T_4 and/or free T_4 without T_3 alterations; 2) excessive response of TSH to the TRH challenge test in 10% and decreased response in 25% of the patients; 3) high levels of antithyroid antibodies present in 15% of the cases; and 4) high concentration of TRH in the cerebrospinal fluid of depressed subjects.

There is general consensus that small changes, even within the normal range, of the levels of thyroid hormones among depressed patients have significant effects in the brain functioning and can be important in the understanding of the biological bases of depression.

The hypothesis that a decrease in the thyroid function is accompanied by an antidepressive response implies that relative increases in the thyroid function are associated with abnormal mood states. This hypothesis derives from the findings of high plasmatic levels of T_4 and from the 'blunted' response of TSH to TRH, indicating a mild degree of hyperthyroidism. The probable increase in the secretion of hypothalamic TRH would be triggered by the dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis in depression.

However, 15% or more of depressed patients have minimal thyroid insufficiency with evidence of an autoimmune thyroid disease, suggesting a 'brain hypothyroidism' without the presence of systemic hypothyroidism. This would occur probably due to the conversion of T_4 into T_3 in the brain by the inhibition of type II deiodinase, caused by an increase of cortisol and/or a decrease in the T_4 transporter through the blood-brain barrier.[2,11] We observed that the alterations in the HPA axis are proposed as an etiology for both the high and low thyroid alterations found in cases of depression.

More recently, it has been also hypothesized that alterations in the HPT axis in non-treated depressions can be partially explained by serotonin and/or noradrenalin brain alterations and that the use of T_3, at a certain degree, can revert this alteration.[11,60] And it has been demonstrated the fundamental role of T_3 in the noradrenergic neurotransmission, confirming the close relation between the thyroid action and depressive disorders. Although instigating, this research line comprises, yet, few and small studies, and should be amplified and have their findings confirmed.

Some authors suggest routine investigation of thyroid hormones when treating depressed patients,[23] whereas others do not recommend it[75] due to the low incidence of thyroid alterations found in depressive pictures. However, it is highlighted the importance of assessing the thyroid gland in those cases of resistant depression and rapid cycling.[9]

There is still much to be understood, as thyroid hormones exert their important influence in the synthesis and activity of G-proteins in the adult brain of mammals.[4] The activity of adenilcyclase is decreased when noradrenalin is applied into the brain of rats with hypothyroidism, indicating an impairment in the transduction of the neuronal signal via adenilcyclase in hypothyroidism.[76] These data suggest that the thyroid condition influences the brain intracellular signaling routes. The studies by Iniguez et al[77] demonstrated that brain thyroid hormones in rats regulate the RC3/neurogranin gene. This gene is a substract of a C/protein kinase and it is probably involved in the hyppocampal activity.[4] It was also ob-

served in hyperthyroidism an anatomic decrease in the density of dendrites of CA1 cells of rats' hippocampus [78]. Therefore, several observations highlight the close relation between sites and actions involved in mood alterations and the condition of thyroid function. It is certainly clear the need of a better understanding of the mechanisms involved in this relation which is expected to arise from new researches, provided medical sciences become interested again in this important psychoneuroendocrinological route.

Most studies about thyroid hormones in depression are more than twenty years old, some of them having good methodological designs but few participants. Knowing that depression is a heterogeneous disorder, that patients are characterized phenomenologically (without biological markers) and that diagnostic criteria have changed over time, the results examined in this review should be cautiously interpreted. We believe that the importance of the study on the relation between depressive disorders and the thyroid function has become very clear and has been demonstrated that the initial findings should be reassessed to favor more consistent scientific evidence.

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Correspondence:
Saint-Clair Bahls
R Carneiro Lobo, 570 conj. 1403, Batel
80240-240 Curitiba, PR, Brazil
E-mail: scbahls@superig.com.br