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Bipolar disorder, cognitive functioning and hypothalamic-pituitary-thyroid axis

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The hypothalamic-pituitary- thyroid axis (HPT) in relation to bipolar disorder (BD) and neuropsychological functions has been studied little in the field of psychoneuroendocrinology. The aim of this study is to review the current status of the following subjects: (1) cognitive dysfunctions in BD as well as their hypothetic etiology; (2) response of the HPT axis in each phase of BD, and finally, (3) the connection between alterations in HPT and neuropsychological deficits.

After a careful analysis of the scientific literature, we conclude that more systematic research is needed because most of the issues, such as the role of HPT in BD and the implication of HPT in neuropsychological deficits, still remain unclear.

Key words:
Bipolar disorder. Hypothalamic-pituitary- thyroid axis. Neuropsychological functions.

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Trastorno bipolar, funciones cognitivas y eje hipotalámico-pituitario-tiroideo

En el campo de la Psiconeuroendocrinología, el eje hipotalámico-pituitario-tiroideo (HPT) ha sido un aspecto poco estudiado en relación con el trastorno bipolar (TB) y las funciones neuropsicológicas. El objetivo de este estudio es revisar el estado actual de los siguientes temas: (1) las disfunciones cognitivas en el TB, así como la etiología de las mismas; (2) la respuesta del eje HPT en las distintas fases del TB y, finalmente, (3) la conexión entre alteraciones del eje HPT y déficits neuropsicológicos.

Del análisis pormenorizado de la literatura científica se desprende que se necesitan más investigaciones istemáticas puesto que la mayoría de los estudios sobre el papel del HPT en el TB y la implicación del eje HPT en los déficits neuropsicológicos muestran resultados discrepantes.

Palabras clave:
Trastorno bipolar. Hipotalámico-pituitario-tiroideo. Funciones neuropsicológicas.

INTRODUCTION

Bipolar disorder (BD) is an alteration of the mechanisms that regulate the mood state and is characterized by alternating periods of manic, hypomanic, and depressive episodes and mixed states. Its prevalence in the general population reaches 4.4% if the mildest forms are included[1;2] and may even reach 6.5% if the atypical forms are included.[3] Its pathophysiology is complex and has not yet been clarified. Even so, research has been aimed towards the study of the neurotransmission mechanisms, neuroanatomical and neurofunctional variables as well as neuroendocrine aspects. Regarding the latter, the hypothalamic-pituitary-adrenal axis (HPA) has been studied the most in the pathophysiology of both unipolar and bipolar depression.[4-6] The hypothalamic-pituitary-thyroid (HPT) and gonadal (HPG) axis have generated more discreet and less conclusive scientific production.

Cognitive dysfunctions in bipolar disorder

Any specialist in BD knows that the statement by Kraepelin on the inter-episodic recovery in patients with BD is almost a myth.[7-10] Both the investigation and the clinical practice show that cognitive deficits are considered one more factor that is a predictor of the evolution of the disorder and psychosocial functioning.[8;9;11]

Verbal memory is one of the cognitive domains most affected and mentioned in the literature.[7-9;12;13] This deficit persist even in prolonged periods of euthymia, suggesting

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that it is a marker of risk of the disorder. Even more, recent studies have proposed it as a cognitive endophenotype since it is also present in first degree relatives.[14;15]

Regarding executive functions, the existence of prefrontal alterations have been mentioned.[16-18] In addition, the study of Kolur et al.,[19] performed in a sample of young patients, also suggests that it may be a risk marker. Finally, the systematic review of Daban et al., [20] that compared executive function in schizophrenic and bipolar patients, concluded that both groups had problems with cognitive flexibility but that the bipolar patients had better performance in abstraction and formation of concepts.

In summary, both verbal memory dysfunctions and executive dysfunctions are as possible cognitive endophenotypes for bipolar disorder.

Etiology of cognitive dysfunctions in bipolar disorder

These dysfunctions can be grouped into 3 categories: (a) genetic factors, (b) environmental factors and (c) factors associated to the disease course per se.

a) genetic factors: introduction of endophenotypes is making it possible to perform a carefully done study of the genes involved in BD.[21] Several studies[22-24] and systematic reviews[14;15;25] that indicate that first degree relatives who are not affected by BD also have dysfunctions in different cognitive domains.

b) environmental factors: It has been demonstrated that comorbid consumption of addictive substances not only worsens but also accelerates cognitive deterioration.[26;27] Another critical endpoint is the medication that could be contributing to a certain degree to the cognitive deterioration observed. Although psychodrugs could be affecting some aspects of cognition, it does not seem to be the first cause of deterioration.
Finally, the study of Savitz et al.[28] stresses the need to control variables related with childhood traumas (e.g. sexual abuse) since they interfere with verbal capacity, visual memory, verbal fluency and cognitive flexibility.

c) factors related with the disease course: variables such as interepisodic functioning,[29-31] psychotic symptoms[12;20;32-34] and course and severity of the disorder[10;13] could also contribute to the cognitive deterioration.

Currently, the debate on the explanatory hypotheses of the cognitive deterioration resolves around two hypothesis: hypotheses of neurodevelopment vs. neurodegenerative. [35] Based on the hypotheses that we choose, each one of the factors described would have a different explanatory weight in the cognitive deterioration.

The thyroid axis in bipolar disorder

Subclinical hypothyroidism and rapid cycling

Subclinical hypothryoidism (SCH) is a condition which has been related with rapid cycling (RC)[36] and female gender since the beginning.[37] However, other studies[37-39] have not found any relationship between SCH and RC. In fact, Joffe[38] had already reported that this condition was associated more to treatment duration with lithium than to the course of the disease itself (RC vs. No RC). It is true that prophylactic treatment with lithium reduces iodine uptake in the thyroid gland and the conversion of tetraiodothyroine (T4) to triiodothyronine (T3).[40] In fact, the studies that include patients who have never been exposed to lithium do not find differences in the prevalence of SCH in the RC groups vs. no RC ones.[41] Along the same line, Zhang et al.[42] compared two samples of patients: one receiving prophylactic treatment with lithium versus another sample without lithium or carbamazepine. The group that did not receive lithium had lower prevalences of SCH (CI: 6.3%-10.8%) versus those treated with lithium (CI: 28%-32.1%). Bauer et al.[43] suggested a very convincing hypothesis that postulates that individuals with RC have high susceptibility to stressants, so that there is no reason for RC and no RC to be differentiated regarding the thyroid function until the former are subjected to antithryoid agents such as lithium or carbamazepine. The Gyulai et al. study[44] tested this hypothesis, comparing the effects of short-term lithium treatment in a sample of patients and another sample with healthy controls. In the baseline evaluation, neither group differed in regards to the HPT axis values and they had an adequate negative feedback to the TRH stimulation test. After the lithium treatment, the RC patient group had superior levels of TSH compared with the controls and an exaggerated response with the TRH stimulation test. Such variations were not a consequence of emotional status, or lithemias, treatment duration.

The thyroid axis in the acute phases of BD

- *Mania and mixed states.*
The Zarate et al. [45] and Chang et al.[46] studies compared two samples: manic vs. mixed states, without a control group and both obtained a thyroid profile of the mixed patients characterized by elevated levels of TSH in regards to the manics. However, they differed in regards to the thyroxine level concentrations (T4). Specifically, Chang [46] found a lower concentration in the mixed patient group in comparison with the manics. Both studies timidly insinuate that mania and the mixed states not only differ regarding symptoms but also their pathophysiology. However, a recent study of Cassidy et al.[47] did not find differences in the thyroid profiles between manics and mixed.

- *Depression.*
  Musselmen and Nemeroff[48] have summarized the levels on which the thyroid dysfunctions were found in patients with depressive episodes:
  1. Alterations in TSH when responding to TRH.[49;50]
  2. Elevated abnormal prevalences of anti-thyroid antibodies.[51;52]
  3. Elevated concentrations of TRH in LCR.[53;54]

  In regards to response to antidepressant treatment, there are studies that use TSH levels as predictors of good response to treatment. It seems that low levels of free thyroxine (T4-F) and high levels of TSH, within the normal ranges, predict poor response in the first treatment days and, complimentarily, high levels of T4-F and low levels of TSH are associated to rapid resolution of the depressive episode.[55] Frye et al.,[56] in a longitudinal study that evaluated prophylactic treatment with lithium versus carbamazepine, found that there were lower levels of T4-F in the lithium phase that were associated with greater affective instability (= more episodes) and greater severity of depressions. Hatterer et al.[57] also obtained similar results, but with levels of T3. In fact, it seems that depressions with melancholic traits or that are treatment resistant are those most associated to subclinical thyroid dysfunctions.[58] Finally, Haggerty[59] hypothesizes that SCH decreases the threshold for the occurrence of depression.

Is there a connection between thyroid disorders and cognitive ones?

Thyroid hormones (TH) are essential for brain development, intervene in glial proliferation, myelinization and in synthesis of enzymes for the formation of neurotransmitters. [60] Thus, the deficit of these hormones in prenatal periods causes profound mental retardation and cretinism. In the adult stage, the implication of TH deficit in cognition (a) is well-established if there is evident hyperthyroidism. However, (b) in the cases of SCH, the validity of this statement is dispelled.

a) (a) The deficits recorded in evident hypothyroidism are: memory, general intelligence, attention and concentration, psychomotor speed, visuo-perceptive skills and constructive skills.[61] In addition, in elderly patients, hypothyroidism may be a cause of dementia (or pseudodementia).[61]

b) (b) In regards to SCH, there are discrepancies on different levels: (1) if SCH really produces cognitive deficits and (2) if these deficits –if they exist - are reversible with replacement treatment (T4 or combination of T3/T4).

While the oldest studies seem to favor the existence of cognitive alterations in SCH, the most recent ones refute this and they suggest that replacement therapy is not useful to improve cognitive functions.

Standing out among the studies in the 1980s and 1990s is that of Haggerty et al.,[62] who found neuropsychological alterations with poor performance in verbal memory, visuo-spatial and selective attention tasks. Furthermore, in another previous study, Haggerty et al., [62] reported that these deficits are partially reversible with levothyroxine. Nystrom et al.[63] also found difficulties on the level of information processing speed and immediate visual recall. The patients of the Monzani study[64] also improved after 6 months of replacement treatment, when they initially had worse scores for attentional capacity and immediate visual and verbal recall.

Regarding the most recent studies, the investigation of Bono et al.[65] did not find a relationship between the TSH levels and cognitive variables and therefore there was no positive effect of treatment with levothyroxine. Improvement was found in posttreatment verbal fluency, but this did not correlate with the changes in the TSH levels. The Jorde et al. study[66] follows the same line, but they evaluated a larger sample and also included a control group with double-blind treatment administration. The groups no longer differed on the baseline level, and the replacement treatment also did not cause improvement in the SCH group, except for clinical symptoms. It should be mentioned that the TSH ranges for the SCH group were between 3.5-10 mLU/l. Therefore, there is no reason to extrapolate these results to SCH with more elevated TSH levels.

CONCLUSIONS

The principal conclusions of this review are summarized in table 1.

The principal purpose of this review has been to clarify up to what point alterations in the HPT axis could be related with the course of the BD per se and to the cognitive deterioration associated to bipolar patients.

In regards to point 1, the cognitive defects and BD, it can be stated that they are two aspects that are almost inseparable and that they are repeated as a *leitmotiv* in a large percentage of patients (40-60%), above all verbal memory and executive functions deficits.[10] However, the etiology of this deterioration has still not been well established[35] (point 2).

Point 3: In regards to the relationship of the TH with cognition and mood regulation, different brain mechanisms are proposed through which the THs exert their effect. In the case of mood modulation, there are different hypotheses that support that the action of the thyroid hormone interacts with the noradrenergic[68] and serotoninergic system of the

Table 1 Principales soluciones

Conclusions	References
1. BD is associated to cognitive deterioration. Verbal memory and executive functions appear as the most effective ones.	Zubieta y cols[7]; Martínez-Arán y cols[8,9]; Mur y cols[67]
2. The origin of this deterioration could respond to both neurodevelopment as well as neurodegenerative aspects.	Goodwin y cols[35]
3. The TH could be exercising its action on cognition and regulation of mood through different biological substrates	Whybrow y Prange[68]; Bauer y Whybrow[69]; Smith y cols[70]
4. The HPT axis as a biomarker for bipolar disorder still does not have sufficient data in its favor.	
5. Some methodological limitations of the study do not make it possible to establish reliable conclusions	Wehr y cols[37], Joffe y cols[38], Oomen y cols[39], Chang y cols[46]
6. There is little evidence that the thyroid dysfunctions observed in patients with BD contribute to the cognitive deterioration (especially verbal memory) that is associated to the disease.	Prohaska y cols[71]; Prohaska y cols[72]

CNS. [69] Even more, this could be the biological substrate that would explain the effectiveness of the TH replacement treatment (levothyroxine) as coadjuvant therapy for the treatment of euthyroid patients with resistant BD (rapid cycling)[73;74] and resistant bipolar depression.[75]

In regards to cognition, the review of Smith et al.[70] proposes that TH would act on the cholinergic system on the level of the basal forebrain and hippocampus. In this sense, the TH in the bipolar disorder has been shown to be useful to decrease the amnesic effects of electroconvulsive therapy and to accelerate the effects of this treatment.[76]

Point 4: The SCH is the thyroid dysfunction most associated to BD. Approximately 30% of the patients treated with lithium develop this condition. [42] One of the hypothesis that has been verified is that of the RC and SCH proposed by Bauer et al.[43] and verified by Gyulai et al.[44] Even though this study manifests that the RC is associated to a latent hypofunction of the HPT axis, the directionality of this relationship (RC and SCH) is still under debate.

When we focus on studies that have tried to provide a profile of the response of the axis in the acute phases of BD, non-specific heterogeneous responses are also obtained[45;46] and even negative results. [47] Thus, the idea that this axis may function as a biomarker is still very incipient.

Point 5: In any event, it is difficult to establish any solid conclusion considering that some of the studies mentioned have some methodological limitations: Lack of a control group,[38;39] retrospective design and without comparison of control group, [37] differences in age between groups and lack of monitoring of the lithium doses with objectivation of lithemias.[46]

Point 6: According to what we know and have reviewed, there are few studies that include the three aspects herein mentioned (SCH, BD and cognitive deficits). Prohaska et al.[72] carried out research in which they proposed that part of the cognitive alterations produced by lithium, and especially verbal learning, were a consequence of the drug on the functioning of the thyroid axis. The high levels of TSH correlated with low scores on the verbal learning test and in addition, no correlations were established between lithemias and the scores on this test. According to this hypothesis, it could also be expected that treatment with thyroxine would reverse these deficits.[71] Thus, if we apply this same reasoning, patients diagnosed of BD and with treated SCH do not necessarily have to have a greater cognitive deterioration than those without this dual diagnosis.

Finally, in spite of the fact that in this review it was not possible to gather sufficient conclusive evidence on the role of the HPT axis in cognition and BD, signs were found on the existence of a subgroup of patients with high susceptibility in this endocrine axis. If this susceptibility is prior to the onset of the disorder, if it is self-limited to the acute phases or if it is a consequence of the evolution itself of the disorder must still be clarified. It is also not known if it could be a marker of severity, resistance or atypicity.

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