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Hypothalamic–pituitary-end organ function in women with bipolar depression

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Summary
Disturbance of each of the three hypothalamic–pituitary-end organ systems [hypothalamic–pituitary–thyroid (HPT), –adrenal (HPA), and –gonadal (HPG)] has been reported in depressive disorders. Little is known about potential reciprocal interaction among the three HP-end organ systems in patients with depressive disorders. The present pilot study examined selective HPA and HPG hormones in a detailed time series in women with bipolar disorder (depressed type) before and after treatment with levothyroxine (L-T4), and in matched control subjects. Six medically stable, euthyroid, premenopausal women with bipolar depression, and 5 age-matched controls underwent overnight blood sampling from 2100 to 0900 h for measurement of adrenocorticotropic hormone (ACTH), cortisol, luteinizing hormone (LH), and estradiol every 15 min. Bipolar patients underwent a second overnight blood sampling procedure following 7-weeks of open-label add-on treatment with L-T4. Results revealed lower baseline cortisol parameters in bipolar patients in comparison to control subjects, while ACTH, LH, and estradiol parameters were similar. Thyroid hormones (TSH, free and total T4) were not correlated with any of the HPA or HPG hormones. ACTH and cortisol levels were correlated in control subjects, but not in bipolar patients. After L-T4 treatment, thyroid hormones increased significantly and depression scores significantly declined. No significant changes in HPA or HPG hormones parameters were observed, although the small sample size may have limited results. Upon visual inspection, ACTH and cortisol appeared to decrease after L-T4 treatment, while estradiol appeared to increase. These pilot data suggest lower levels of cortisol in women with bipolar depression, unlike previously published studies that reported higher cortisol in patients with depression. The data also suggest reciprocal changes in the HPA and HPG axes

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upon pharmacological modulation of the HPT system, although whether this change was due to the L-T4 treatment or the improvement of depression is unknown. The results are preliminary, and require replication in larger samples.

1. Introduction

The relationship between affective illness and endocrine systems has generated considerable interest in recent years. Investigations into the pathophysiology of depressive disorders suggest the involvement of each of the three hypothalamic–pituitary-end organ systems; hypothalamic–pituitary–thyroid (HPT) (Kirkegaard and Faber, 1998), hypothalamic–pituitary adrenal (HPA) (Holsboer 2001; Ising et al., 2005), and hypothalamic–pituitary–gonadal (HPG) (Young and Korszun, 1998). However, most of the studies reported in the literature have focused on a single HP-end organ axis, rather than exploring the interactions among the three endocrine systems.

Our group, among others, has presented several lines of evidence suggesting that thyroid hormones affect brain functions and interact with other neuroendocrine systems (Bauer et al., 2003). Disorders of the thyroid gland are associated with mood and cognitive dysfunction, and affective disorders are associated with abnormalities in the HPT axis (Bauer et al., 2003). Furthermore, adjunctive thyroid hormones, in both hypothyroid as well as euthyroid patients, have been shown to improve the course of depression (Bauer et al., 1998, 2002, 2005; Bauer and Whybrow, 1990; Baumgartner et al., 1994). Basic research indicates central mechanisms by which the HPT and HPA systems interact, suggesting that relationships may exist between the two systems in depressive disorders (Musselman and Nemeroff, 1996; Redei, et al., 1995).

Cortisol hypersecretion in depression has been reported by some groups (Cervantes et al., 2001; Linkowski et al., 1988), but not others (Posener et al., 2004). Unfortunately, only two studies have separately examined unipolar from bipolar depressed subjects. Those studies found hypersecretion of cortisol during both depressed (Cervantes et al., 2001; Linkowski et al., 1988) and manic phases (Cervantes et al., 2001), as well as abnormal response to the dexamethasone/CRH challenge (Watson et al., 2004), suggesting HPA dysfunction is a trait marker in some bipolar patients. However, a number of other co-occurring factors appear to affect HPA activity, including gender (Uhart et al., 2006), (Young and Ribeiro, 2006), age (Kudielka et al., 2004; Traustadottir et al., 2005), and BMI (Pasquali et al., 1998), which may limit interpretation of results in subjects unmatched for gender, age, or BMI.

Less is known about HPG axis activity in women with depressive disorders. Studies utilizing single-time-point hormone measures have reported no differences between women with depression and controls for luteinizing hormone (LH) (Young and Korszun, 2002). With respect to estradiol in depressed women, there is one report of lower levels (Young et al., 2000) and one report of higher levels (Bao et al., 2004). Previous published data on circadian HPG activity in premenopausal depressed women is limited to one study reporting slower frequency dysrhythmic LH pulsatility (Meller et al., 2001). For the most part, data collected to date suggest normal HPG functioning in depression, despite hypercortisolemia in some subjects (for review, see Young and Korszun, 2002).

In this study, we explored ultradian HPA and HPG activity in a small sample of bipolar depressed and matched healthy control women. The HPA and HPG activity of the bipolar depressed women was assessed before and after modulation of the HPT axis with 7 weeks of L-T4 treatment.

2. Methods

2.1. Study design

This study was part of a prospective, open-label 7-week trial in women with bipolar disorder (Bauer et al., 2005) approved by the UCLA institutional review board. The protocol included overnight blood sampling for hormone levels and positron-emission tomography (PET) in bipolar depressed premenopausal women and matched healthy control subjects. Data on PET and mood changes associated with L-T4 are reported elsewhere (Bauer et al., 2005). Herein, we report baseline hormone parameters in bipolar and control subjects, and post-treatment hormone parameters in bipolar patients.

2.2. Participants

Bipolar patients underwent informed consent prior to eligibility screening. Study inclusion criteria were good general health, euthyroid status (TSH 0.3–4.7 μIU/mL), a score of $\geqslant$15 on the 21-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1980), and a diagnosis of bipolar disorder (depressed phase) unresponsive to at least 6 weeks of antidepressant treatment. All patients had received the same antidepressant during the 6 weeks prior to study entry, with no changes in dose during the 3 weeks prior the study entry or during study treatment). Study exclusion criteria were psychotic features or history of psychotic disorders, organic brain disorder, thyroid adenoma, unstable medical illness, endocrine disorder, cardiovascular disease, intake of thyroid hormones, and suicidal risk.

Control subjects underwent the same physical and psychiatric screening procedures as the bipolar research subjects, after informed consent. Subjects were excluded if they had current or past mental disorders, intake of any hormonal or psychotropic agents, history of endocrine, cardiac, or other severe medical disease, and family history of psychiatric disorders.

Pregnancy or lactation, children within the past year, and women of childbearing potential not using contraception were excluded from both groups of subjects. All bipolar