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Neuroendocrine abnormalities associated with untreated first episode patients with major depressive disorder and bipolar disorder

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ABSTRACT

There are few studies that explore simultaneously the relationship of neuroendocrine hormones of the HPA, HPT and HPG axes with major depressive disorder (MDD) and bipolar disorder (BD). The aim of this study is to examine the relationship of neuroendocrine pathways with affective disorders by comparing the differences in measures of neuroendocrine function between untreated first episode patients with MDD and BD. A cohort of 679 MDD and 83 BD patients was recruited. Thyroid stimulating hormone (TSH), triiodothyronine (T3), free triiodothyronine (FT3), thyroxine (T4), free thyroxin (FT4), cortisol (COR), adrenocorticotropic hormone (ACTH), estradiol (E2) and testosterone (T) were determined by chemiluminesent immunoassay for all patients. COR and ACTH were both significantly higher in the MDD group than those in BD group. The incidences of high secretion of ACTH and COR, and low thyroid hormone secretion were significantly greater in MDD patients than in BD patients. Decreased T secretion was more common in BD than MDD patients. ACTH was significantly positively correlated with HAMD total score and negatively correlated with FT3 in MDD patients. FT3 and FT4 levels were significantly negatively correlated with the somatoform factor score of HAMD in MDD patients. Untreated first episode patients with MDD have a hyperactivity of the HPA axis, lower HPT compared with BD patients. BD patients had reduced testosterone secretion. These findings indicate that ACTH, FT3 and FT4 could be used as markers for severity and symptoms of untreated first episode patients with MDD.

1. Introduction

There has been a growing interest in how neuroendocrine hormones may have a role in the biological mechanism(s) of major depressive disorder (MDD) (Eser et al., 2006). The most extensively studied neurosteroid is the glucocorticoid cortisol, the final product of the neuroendocrine Hypothalamic–Pituitary–Adrenal (HPA) axis. Excessive exposure to cortisol has been found to have neurotoxic effects; therefore dysregulation of the HPA axis, attested by elevated circulating levels of corticotropin (ACTH) and cortisol (COR), is one of the major neuroendocrine abnormalities observed in depression (Lloyd and Nemeroff, 2011). COR hypersecretion has been proposed as a marker of trait vulnerability to depression, and thus may represent an illness endophenotype (Beluche et al., 2009; Bhagwagar and Cowen, 2008).

There is evidence that abnormal levels of free thyroxine (FT4) or thyroid stimulating hormone (TSH) are associated with either current or lifetime MDD (Forman-Hoffman and Philibert, 2006; Williams et al., 2009), and that antidepressant treatment might partly reverse this dysfunctional state (Fountoulakis et al., 2006). Therefore dysfunction of the hypothalamic-pituitary-thyroid (HPT) system in MDD suggests that serum thyroid hormones may also have potential as biomarkers (Fountoulakis et al., 2006; Stipcevic et al., 2008).

Besides those of the HPA and HPT axes, other neuroimmunoendocrine markers such as LH, FSH, estradiol and progesterone have been shown to correlate with recovery in MDD, and sex hormone changes might be related to mood improvement (Huang et al., 2008), so the hypothalamic-pituitary-gonadal axis (HTG) may be also involved in the pathogenesis of MDD.

In addition, biological disturbances in the regulation of the HPA axis are believed to play a key role in bipolar disorder (BD) (Goldstein et al., 2009). Previous studies have found higher COR levels in BD patients compared to healthy controls (Deshauer et al., 2003; Rybakowski and Twardowska, 1999).

It is well established that the HPA, HPT and HPG axes may interact.

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The HPA axis can have a negative influence on the HPT axis (Castañeda Cortés et al., 2014); furthermore, hormones pertaining to both HPT and HPA axes may also influence the HPG endocrine axis. This is illustrated by an increase in activity of the HPA axis resulting in diminished activity of the HPG axis (Swaab et al., 2005; Castañeda Cortés et al., 2014). Therefore the question arises whether dysfunction of the three axes could be associated with symptoms in MDD, and also whether dysfunction of the three axes differs between MDD and BD. Even though it is suggested that the range of diurnal variation in COR might differentiate MDD and BD as depressed patients with high diurnal COR slope (i.e. rate of change in COR) were found to have greatly increased likelihood of a hypomanic episode (Becking et al., 2015), there are few studies directly comparing MDD and BD. We have hypothesized that HPA would be negatively correlated with HPT and HPG in MDD – but not BD – groups.

2. Materials and methods

2.1. Subjects

A cohort of 803 patients with MDD who were all first episode and untreated patients, and another 106 patients with BD who were all first diagnosed and untreated patients meeting diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I (First and Spitzer, 2002) were recruited for the present study between 2014–2018 from the Second Affiliated Hospital to Kunming Medical University, Kunming, China. Exclusion criteria included: (1) having evidence of mental retardation, any pervasive developmental disorder or a major non-psychiatric medical condition (e.g. diabetes, neurologic disease, CNS damage,); (2) having comorbid diagnoses of Obsessive Compulsive Disorder, Post-traumatic Stress Disorder (PTSD), alcohol-related diseases, or a history of psychosis; (3) having a history or current symptoms of thyroid disorders, gynecological disease, or endocrine disorders; (4) pregnant or lactating women, menstrual period or peri-menopausal period women, a history of irregular menstrual cycle; (5) having taken antidepressant medication, hormones, oral contraceptives or systemic, topical or inhaled steroids, or other medicines which could affect thyroid functions in the 3 months before the study.

The study was carried out in accordance with the latest version of the Declaration of Helsinki, and was approved by the Ethics Committee of the Second Affiliated Hospital to Kunming Medical University. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

All subjects were inpatients, and were given alprazolam 0.4–0.8 mg for sleep if the patient had insomnia. No other medications were provided before blood withdrawal. Blood was taken in the morning after the patient was hospitalized, in order to ensure that patients have a certain adaptation to the environment. Twenty milliliters of venous blood were collected from each subject for further analysis. All blood collections were performed at the same time of day (8:00a.m.–9:00a.m.).

2.2. Procedures

2.2.1. Clinical and cognitive measures

After diagnostic eligibility was determined, the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), Hamilton Rating Scale for Anxiety (HAMA) (Hamilton, 1959) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were completed by a trained member of staff to assess current mood state.

2.2.2. Hormone determination

The assessment of hormone variables was undertaken at a single point in time (8:00 am-9:00 am). As there is significant variation in the literature in the timing of blood draws for COR, ACTH, TSH, T3, FT3, T4 and FT4 assays, collection at multiple time points is ideal for establishing reliability of hormone levels. In order to deal with this limitation, the blood samples for serum analyses in this study were collected between 8:00 am and 9:00 am as this is the time when hormone levels are at their highest point in the diurnal cycle (Hucklebridge et al., 2005).

Plasma COR and ACTH levels were measured using the chemiluminescence immunoassay kit (AutoLumo A2000) according to the manufacturer's instructions. A range for healthy subjects of 4.26–24.85 u g/dl was used as the normal level for COR, and a range for healthy subjects of 7.20–63.40 pg/ml was used as the normal level for ACTH.

Plasma TSH, T3, FT3, T4, FT4 levels were measured using the chemiluminescence immunoassay kits (LIAISON X20) according to the manufacturer's instructions. The normal levels for TSH, T3, FT3, T4, FT4 for healthy subjects were 0.27–4.20 mIU/L, 0.76–2.20 u g/L, 3.39–7.14 pmol/L, 45.00–126.00 u g/L, 10.29–21.88 pmol/L.

Plasma estradiol (E2) for females and testosterone (T) for males were measured using eletrochemiluminescence immunoassay kit (Cobas 6000) according to the manufacturer's instructions. The normal level of E2 for healthy subjects was $\geq$5.00 pg/ml threshold, and for T was 2.49–8.36 ng/ml for males.

All the tests were done, and all the normal ranges of the above hormones for healthy subjects were provided by the Nuclear Medicine Department, the Second Affiliated Hospital to Kunming Medical University, who undertake these assays routinely.

2.2.3. Definition of abnormal hormone secretion

According to the normal ranges of hormones, the definitions of abnormal values of hormones were made as follows:

2.2.3.1. Increased thyroid hormone secretion (ITHS). Increased T3 (> 2.20 ug/L), increased FT3 (> 7.14 pmol/L), increased T4 (> 126.00 ug/L), increased FT4 (> 21.88 pmol/L), decreased TSH (< 0.27 mIU/L), at least one item abnormal.

2.2.3.2. Reduced thyroid hormone secretion (RTHS). Decreased T3 (< 0.76 ug/L), decreased FT3 (< 3.39 pmol/L), decreased T4 (< 45.00 ug/L), decreased FT4 (< 10.29 pmol/L), increased TSH (> 4.20 mIU/L), at least one item abnormal.

2.2.3.3. Increased secretion of ACTH and COR (ISAC). Increased ACTH (> 63.40 pg/ml), Increased COR (> 24.85 ug/dl), at least one item abnormal.

2.2.3.4. Reduced secretion of ACTH and COR (RSAC). Decreased ACTH (< 7.20 pg/ml), decreased COR (< 4.26 ug/dl), at least one item abnormal.

2.2.3.5. Reduced E2 secretion (RE2). Since female estradiol E2 fluctuates greatly with the physiological cycle, only samples with lower than 5.00 pg/ml of E2 menopause was selected as data for E2 secretion reduction in this study.

2.2.3.6. Increased testosterone secretion (ITS). Testosterone above 8.36 ng/ml.

2.2.3.7. Reduced testosterone secretion (DTS). Testosterone lower than 2.49 ng/ml.

2.3. Statistical analyses

Statistics were performed using the SPSS 17.0 software (Statistical Package for Social Sciences, SPSS Inc). ANOVA or X^2 tests were performed to test for differences in socio-demographic variables. Hormone levels in the two disease groups were compared by t tests, and the

incidences of abnormal hormone secretion in two groups were compared by X2 test. Kolmogorov-Smirnov test was used to determine the normal distribution of all hormones. Pearson's correlations between all hormone indicators, demography, seven symptom dimension scores and total scores of HAMD, two symptom dimension scores and total scores of HAMA, total scores of YMRS were calculated to explore their interrelatedness. All analyses used two-tailed estimation of significance. Power analysis for comparisons using the independent samples *t*-test indicated that when $\alpha = 0.05$, $\beta = 0.1$, a threshold of at least 238 cases for MDD, and 27 cases for BD was required. All statistically significant P values were set at < 0.05.

3. Results

3.1. Demography

After applying exclusion criteria, 679 patients with MDD and 83 patients with BD underwent further study.

According to the sample calculation, the power analysis showed that the statistical power was 90%. Kolmogorov-Smirnov tests showed that all investigated hormones in 762 total sample number were in normal distribution (TSH: p = 0.067; COR: p = 0.20; T3: p = 0.063; FT3: p = 0.18; T4: p = 0.071; FT4: p = 0.11; ACTH: p = 0.13; E2: p = 0,087; T: p = 0.073).

For MDD patients, 263 (38.7%) were male and 416 (61.3%) female, the mean age 31.4 ± 8.7 years. For BD, 39 (47%) were male and 44 (53%) female, the mean age 24.8 ± 4.5 years. Of BD, 50 patients were bipolar II who were currently in a depressive episode, 23 patients were bipolar I who were currently in a manic episode and another 10 patients were bipolar I who were currently in a mixed episode. X^2 test showed that there was no significant difference for gender between two groups ($X^2 = 2.106$, P = 0.155). *t*-test showed that there was significant difference for mean age between two groups (t = 6.798, P < 0.001).

The mean durations of education for MDD was 15.8 ± 3.9 years, and for BD was 13.9 ± 2.5 years. The illness duration for MDD was 1.56 ± 2.9 years, and for BD was 3.87 ± 3.45 years.

3.2. Hormones secretion differences between MDD and BD groups

In order to account for the influence of age on hormonal differences, we compared the differences using age as covariate. As shown in Table 1, COR and ACTH were both significantly higher in the MDD group than the BD group. However, other hormones did not demonstrate significant differences between the two groups. There was no subject with E2 above the normal range.

3.3. The incidences of abnormal hormone secretion between MDD and BD groups

After comparing the absolute values of hormones, we compared the incidence of abnormal hormone secretion between the two groups. X^2 tests demonstrated that the incidence of increased ACTH, COR and reduced thyroid hormone was significantly greater in MDD patients than in BD patients. Decreased T secretion was more common in BD than MDD patients, as shown in Table 2.

Table 1
Hormones secretion differences between MDD and BD groups.

Hormones	MDD	BD	t	P
COR (ug/dl)	25.12 ± 3.42	21.05 ± 2.14	2.124	0.036
ACTH (pg/ml)	45.46 ± 11.78	26.59 ± 9.21	2.406	0.018
TSH (mIU/L)	2.54 ± 0.94	2.37 ± 0.87	0.166	0.685
T3 (ug/L)	0.98 ± 0.22	1.03 ± 0.31	0.364	0.548
FT3 (Pmol/L)	4.47 ± 1.26	4.44 ± 1.29	0.01	0.919
T4 (ug/L)	67.838 ± 13.91	68.307 ± 14.25	0.013	0.911
FT4 (Pmol/L)	13.387 ± 1.67	13.207 ± 1.79	0.069	0.794
E2 (pg/ml)	71.48 ± 31.85	63.49 ± 29.46	0.107	0.745
T (ng/ml)	2.786 ± 0.73	0. 925 ± 0.12	4.95	0.061

Table 2
The incidences of abnormal hormone secretion between MDD and BD groups.

	ITHS % (n)	RTHS % (n)	ISAC % (n)	RSAC % (n)	RE2 % (n)	ITS % (n)	DTS % (n)
MDD	1.8 (12/679)	29.6 (201/679)	58.6 (398/679)	5.6 (38/679)	12.98 (54/416)	7.98 (21/263)	12.9 (34/263)
BD	1.2 (1/83)	14.5 (12/83)	34.9 (29/83)	4.8 (4/83)	16.1 (7/44)	3.7 (1/39)	59.3 (23/39)
X^2	0.140	8.423	16.828	0.086	0.408	0.640	36.837
P	0.709	0.004	< 0.000	0.770	0.531	0.504	< 0.000

ITHS: Increased thyroid hormone secretion; RTHS: Reduced thyroid hormone secretion; ISAC: Increased secretion of ACTH and COR; RSAC: Reduced secretion of ACTH and COR; RE2: Reduced E2 secretion; ITS: Increased testosterone secretion; DTS: Decreased testosterone secretion.

3.4. Correlative analysis of hormones secretion and symptoms in MDD and BD groups

Pearson correlation analysis showed that ACTH was positively and significantly correlated with the HAMD total score (r = 0.335, P = 0.004) even after Bonferroni correction (P = 0.032). ACTH was also negatively and significantly correlated with FT3(r = -0.231, P = 0.047)in MDD patients, but after Bonferroni correction there was no significant difference. FT3 and FT4 values were positive significantly correlated with the somatoform factor score in HAMD (r = 0.386, P = 0.003; r = -0.443, P = 0.002) even after Bonferroni correction (P = 0.024; P = 0.016). For BD patients, there was no significant correlation found.

4. Discussion

The present study examined HPA, HPT and HPG function in first episode patients with diagnoses of MDD and BD. The results demonstrated that plasma levels of COR and ACTH were both higher in MDD than BD, especially for COR which was increased over the normal level in MDD patients. One major advantage of the present work over previous studies was that dysfunction of HPA-HPT-HPG axes was based on assessment of abnormal levels across multiple indicators, not on each measure individually, permitting the comparison and correlation of findings between the various axes.

Depression is often conceptualized as a stress-related disorder. Stress sensitivity may be indicated by changes in reactivity of stress response systems, including the hypothalamic-pituitary-adrenal (HPA) axis, which has been implicated as a mediator of stress sensitization and vulnerability to depressive episodes (Oldehinkel and Bouma, 2011). Consistent with our hypotheses, increased COR and ACTH confirmed the well-documented alteration of HPA function in MDD subjects (Burke et al., 2005). With a hyperactivity of the HPA, the incidences of increased secretion of ACTH and COR were significantly higher in MDD patients than in BD patients, confirming again that MDD is associated with higher basal ACTH and COR secretion (Stetler and Miller, 2011). For BD, an abnormality of HPA function was not found in this sample. In our study we directly tested the plasma levels of COR and ACTH, rather than using the dexamethasone suppression/CRH-challenge (DEX/CRH) test (Heuser et al., 1994), though it confirmed that psychiatric patients were prone to an altered glucocorticoid feedback regulation during the acute illness episode, especially for MDD with highest sensitivity, but not for all mental disease, such as posttraumatic stress disorder (PTSD) (de Kloet et al., 2008). These results again supported the link between the abnormalities of the HPA axis and

depression raised by a recent system review (Juruena et al., 2018).

There is evidence suggesting that persistent HPA alterations are associated with increased risk of recurrence of MDD (Appelhof et al., 2006; Chopra et al., 2008). Individuals with recurrent depression were more likely to exhibit elevated COR levels during remission (Bos et al., 2005). Additionally, COR secretion has been identified as a susceptibility factor for late-life depression (Ancelin et al., 2013). Recently in a comparison of psychotic and non-psychotic major depression, cognitive performance was negatively correlated with higher COR, and higher COR was apparent in the psychotic group (Keller et al., 2017). Our study showed ACTH was significantly correlated with the total score of HAMD, suggesting that the severity of depression for untreated first episode patients with MDD was related to the extent of ACTH elevation. Therefore, this evidence suggests hyperactivity of the HPA axis may be a useful indicator of severity in first episode depression.

Even though there were no significant differences in mean values of serum markers of HPT between MDD and BP, our results demonstrate that MDD patients were more likely to have an abnormal reduction in thyroid hormone secretion. It is known that the HPA axis might influence the HPT axis through a negative regulation of thyroid-stimulating hormone secretion mediated by corticotropin-releasing hormone signaling (De Groef et al., 2006), therefore increased function of HPA would result in a hypofunction of HPT. In this present study, ACTH was also significantly negatively correlated with FT3 in MDD patients, consistent with a negative feedback effect of the HPA axis on the HPT axis. A number of other studies have interrogated the relationship between FT4 or TSH and MDD in subjects without autoimmune thyroid disease. Altered thyroid function is often associated with symptoms of MDD (Jackson, 1998), and increased FT4 levels are associated with either current or lifetime MDD (Williams et al., 2009). In this study, FT3 and FT4 levels were positively correlated with the somatoform score of HAMD. Somatoform factor is one of factors in HAMD, and it includes a group of somatic symptoms in depressive episode. Up to now there is no research to show the association of somatic symptoms of MDD with FT3, FT4, so replications studies are also needed to testify that FT3 and FT4 could be a potential biological marker for some symptoms of MDD.

Testosterone can influence neuronal function through binding to intracellular receptors, through modulation of ligand-gated ion channels, and through binding to neurotransmitter receptors (Zarrouf et al., 2009). It is also involved in modeling the developing brain and influences the continuous process of neuronal adaptation to new environmental demands. This present study showed higher incidences of decreased testosterone secretion in BP patients than in MDD patients. Known neuro-behavioural effects of testosterone include actions on sexual function and aggression, and depressed men have lower testosterone (Rubinow and Schmidt, 1996; Ebinger et al., 2009). Sher et al showed that testosterone levels might be related to the course of BD and suicidal behavior, and may predict suicidal behavior in women with bipolar disorder (Sher et al., 2012, 2014). Our result was consistent with these researches, suggesting the association of testosterone secretion in BP.

The current study has a number of limitations. First, the assessment of hormone variables was undertaken at a single point in time (i.e. cross-sectional). As there may be a large number of circadian variation in COR, ACTH, TSH, T3, FT3, T4 and FT4 assays, collection at multiple time points is ideal for establishing reliability of hormone levels. In order to deal with this limitation, the blood samples for serum analyses in this study were collected between 8:00 am and 9:00 am as this is the time when hormone levels are at their highest point in the diurnal cycle (Hucklebridge et al., 2005). In this study, we did not use DEX/CRH test because its application to this study was not approved by our ethics committee because the DEX–CRH test has adverse effects, for instance slight nausea, metallic taste, scraping feeling in the throat, sensation of heat and on rare occasions allergic reactions with shortage of breath (Müller, 2005). Second, despite the fact that our sample in the present study is relatively large, the BD group was substantially smaller than that for MDD. Thus analysis following further division of BD to I and II types was not attempted. Thirdly, because this is a cross-sectional study with first episode and untreated patients, we could not fully exclude a situation in which some depressive episode patients might be diagnosed as having BD in the future. Finally, even though the normal ranges of all tested hormones from healthy subjects were provided by the Nuclear Medicine Department, it would have been valuable to have an additional well-matched healthy control comparison group.

5. Conclusion

In conclusion, this study revealed that untreated first episode patients with MDD exhibited hyperactivity of the HPA axis, lower HPT function compared with BD patients. And BD patients had reduced testosterone secretion. In addition, ACTH, FT3 and FT4 may have potential as markers for severity and symptoms of untreated first episode patients with MDD.

Disclosureand conflicts of interest

The Authors declares that there is no conflict of interest.

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