Background: There have been few neuroendocrinology studies of suicidal behaviors among patients with depression and the results of these studies have been inconsistent.

Aim: To explore the association between the function of the hypothalamus-pituitary-adrenal (HPA) axis and suicidal behaviors in Chinese patients with depression.

Methods: Several measures of HPA functioning in 14 depressed patients who had had suicidal behaviors in the two prior months (‘depressed cases’) were compared to those of 15 depressed inpatients who did not have prior suicidal behaviors (‘depressed controls’): a dexamethasone suppression test (DST), the diurnal changes in serum cortisol levels during a single day before and after 6 weeks of treatment with paroxetine; and 24 h urinary 17-OH cortisol and free corticosterone before and after treatment. The Hamilton Depression Scale (HAMD) was used to measure the severity of depression. Daytime cortisol levels were also assessed in 15 non-depressed controls selected from individuals who had a routine health exam.

Results: There were no statistically significant differences in the 24 h urinary measures of cortisol and corticosterone between depressed cases and depressed controls. In both groups the normal midnight drop in serum cortisol was non-significant prior to treatment but after treatment it became more pronounced. The DST was positive in more of the depressed cases than depressed controls (57% v. 20%, \(\chi^2=4.24, p=0.039\)). The correlation of cortisol serum levels with the HAMD total score and the item scores for hopelessness and suicidal ideation were statistically significant in the depressed case group both before and after treatment, but in the depressed control group these correlation coefficients did not reach statistical significance. The 08.00 h serum cortisol level in depressed cases was significantly greater than the level in non-depressed controls both before and after treatment, but the level in depressed controls was not significantly greater than that in non-depressed controls.

Conclusion: These findings are broadly consistent with those of prior studies about the relationship of depression and the functioning of the HPA axis. There were, however, some differences between depressed patients that did and did not report prior suicidal behavior which may indicate suicide-specific characteristics of HPA axis dysfunction. These differences merit further assessment in larger studies that distinguish patients who have made suicide attempts from those who only report prior suicidal ideation.

1. Introduction

Depressive disorders are among the most common mental disorders and they are closely related to suicide. The majority of individuals who die of suicide have depressive symptoms before they die; international reports estimate that more than 60% of persons who die of suicide have a depressive disorder at the time, and a large, representative study in China found that 35% of suicide decedents met the diagnostic criteria for a depressive disorder at the time of death. In the United States the estimated annual suicide rate in individuals with depression is 85 per 100 000 (eight times higher than the rate in the general US population) while similar estimates from Shanghai suggest that the suicide rate is 100 per 100 000 individuals with depression. Thus, the prevention and appropriate management of suicidal behavior among people with depression is an important component of overall suicide prevention efforts.

Despite the high rates of suicidal behavior in depressed individuals, only a minority of depressed persons actually attempt suicide, so it is important to...
identify which depressed individuals are at highest risk of suicide. Over the last 30 years biological psychiatrists have sought a biomarker that can predict suicidal behavior in depressed individuals. Early studies found decreased levels of the dopamine metabolite homovanillic acid and the serotonin metabolite 5-HIAA in the cerebrospinal fluid of individuals with depression who died of suicide, suggesting decreased presynaptic function of dopamine and serotonin.[4] Recent work has focused on postsynaptic receptor transmission in the central nervous system, as mediated by the hypothalamus-pituitary-adrenal (HPA) axis.[5-7] However, there have only been a few studies on the relationship of suicidal behavior and HPA axis functioning among individuals with depression in China, and the findings that are available have been inconsistent.[8,9] Moreover, to the best of our knowledge, there has been no study in China assessing diurnal fluctuations of cortisol in persons with depression.

To help further clarify the relationships of depressive symptoms, suicidal behavior and functioning of the HPA axis, the current study conducts a dexamethasone suppression test and assesses 24 h urinary and serum cortisol levels in patients with depression who have and have not had prior suicidal behavior both before and after a 6-week course of treatment with paroxetine.

2. Methods

2.1 Study participants

The enrollment of subjects is shown in Figure 1. Patients admitted to the Fourth People’s Hospital of Shantou City from June 2009 to June 2011 who met criteria for a current major depressive episode as defined by the Chinese Classification of Mental Disorders[10] were potential participants in the study. Enrolled subjects met the following criteria: a) a total score of at least 24 and b) a diagnosis of depression. A total of 189 individuals met the study criteria, 104 of whom had no history of suicidal behavior in the past 2 months, and 27 of whom were randomly selected as controls. Of the 85 individuals who had a history of suicidal behavior in the past 2 months, 23 were included in the study as depressed cases. The remaining 352 non-pregnant or non-menstruating individuals who provided informed consent were also assessed. The study was conducted in accordance with the Declaration of Helsinki and all procedures involving human subjects were approved by the institutional review board at the Fourth People’s Hospital of Shantou City.
on the Hamilton Depression Rating Scale (HAMD-17)\[^{11}\] at the time of enrollment; b) no use of antidepressant medication in the three days prior to enrollment; c) not pregnant or menstruating at the time of enrollment; d) no concurrent mental disorder or substance abuse problem; e) no physical condition that could affect the functioning of the HPA axis (e.g., hypothyroid disease, malignant tumor, etc.); f) the ability to cooperate with the intended examinations and assessments; and g) either the patient or the patient’s guardian provide written informed consent.

The presence of prior suicidal behavior was determined by asking the patient the following questions: ‘In the last two months have you experienced any of the following: 1) feeling that life isn’t worth it, discouraged about the future, pessimistic and hopeless; 2) repeatedly thinking of death; 3) wishing you were already dead; 4) often thinking about things related to death; 5) having negative ideas or thoughts of suicide; 6) impulsive self-harm; or 7) suicidal behavior.’ Among the 127 eligible patients, 23 reported some level of suicide-related behavior in the prior two months, including 16 who only reported suicidal ideation and 7 who reported a suicide attempt. These 23 individuals were combined under the rubric of ‘suicidal behavior’ and classified as ‘depressed cases’. Among the 104 depressed patients without suicidal behavior in the prior two months, 27 were randomly selected as the ‘depressed controls’. A ‘non-depressed control’ group of 26 individuals was randomly selected from among individuals receiving routine health checks at the hospital. The baseline assessment (see below) involved multiple blood tests so several selected subjects refused to participate: 9 refused from the depressed cases group, 12 from the depressed controls group, and 11 from the non-depressed controls group. This left 14 depressed cases, 15 depressed controls and 15 non-depressed controls; there were no significant differences in gender and age between selected individuals who did and did not complete the baseline assessment.

All the depressed patients were treated for a minimum of 6 weeks with paroxetine 20 to 40 mg/d and any adjunctive treatments the treating clinician considered appropriate. All 29 depressed patients completed the 6 weeks of treatment and all of them were subsequently followed up 6 months later to determine whether or not there had been a recurrence of suicidal behavior.

This study was approved by the Ethics Review Committee of the Fourth People’s Hospital of Shantou City.

2.2 Assessments

In the non-depressed controls a single blood sample was drawn at the time of their attendance at the outpatient department for a health check, that is, during regular daytime working hours.

Several different assessments were conducted in the two patient groups: a) a 24h urine sample was collected on the day after recruitment and at the end of the six-week treatment period to determine urinary 17-OH cortisol and free corticosterone levels; b) blood samples were collected at 08.00h, 12.00 h, 16.00 h, 20.00 h and 00.00 h on the day after recruitment and on the last day of the 6-week treatment period to assess the circadian rhythm of secretion of cortisol; c) the dexamethasone suppression test (DST) was conducted by collecting blood samples at 00.00 h on the second day after recruitment to measure their baseline cortisol levels, administering 1 mg of dexamethasone orally, and repeating the blood samples at 08.00 h on the day of the test and at 08.00h on the day after the test; and d) the severity of the depressive symptoms was assessed before and after treatment using the 17-item Hamilton Depression Rating Scale (HAMD)\[^{11}\]. The photoluminescence method was used to assess cortisol levels in the samples.

2.3 Analysis

Based on the criteria used by Guo\[^{12}\] in the DST an 80% decrease in the baseline cortisol level 8 hours later (that is, at the first 08.00 h blood draw) was considered normal; that is, anything less than an 80% reduction was considered ‘non-suppression’. Several measures were used from the HAMD: the total score of all 17 items (range, 0 to 54); an anxiety-somatization subscale score that included 5 items (range, 0 to 16); a retardation subscale score that includes 4 items (range, 0 to 14); and single-item scores for sleep problems, hopelessness, and suicidal ideation (range, 0 to 4).

Frequencies, proportions, and means were used to describe the data. SPSS 11.0 software was used for data analysis. Chi-squared tests, Fisher’s Exact tests, t-tests (one-sample and two-sample), repeated measure ANOVA with contrast analysis, and Spearman correlation coefficients were used for comparisons. Statistical significance was considered present when the p-value was less than 0.05.

3. Results

The 14 depressed cases who completed the assessments included 9 males and 5 females with a mean (sd) age of 32.4 (7.5) years and a range in ages from 19 to 54. The 15 depressed controls included 10 males and 5 females with a mean age of 34.7 (6.9) years and a range in ages from 21 to 52. The 15 non-depressed controls included 9 males and 6 females with a mean age of 32.9 (7.3) years and a range in ages from 19 to 54. There were no statistically significant differences in the gender or age of the three groups.
3.1 Comparison of urinary 17-OH cortisol and free corticosterone in depressive patients before and after treatment

As shown in Table 1, the urinary 24 h 17-OH cortisol level and the 24 h free corticosterone level did not differ between the depressed cases and the depressed controls at the time of enrollment. Moreover, after adjustment for the baseline levels, the cortisol levels at the time of the 6-week post-treatment follow-up were not significantly different between the two groups. There was, however, a significant drop in the urinary 24 h free corticosterone level with treatment in both the depressed cases and the depressed controls.

Table 1. Comparisons of 24 h 17-OH cortisol and free corticosterone in urine between 14 depressed cases with prior suicidal behavior and 15 depressed controls without prior suicidal behavior before and after 6 weeks of treatment with paroxetine (mean [sd])

|                      | Before treatment | After treatment | F  | p         |
|----------------------|------------------|----------------|----|-----------|
| 24 h 17-OH cortisol  | (umol/L)         |                |    |           |
| Cases                | 98.5 (8.7)       | 85.1 (7.4)     | 4.12 | 0.053     |
| Controls             | 91.6 (8.2)       | 73.2 (7.2)     | 0.61 | 0.442     |
| statistic            | t=0.26           | F=0.49         |    |           |
| p                    | 0.799            | p=0.489        |    |           |
| 24 h free corticosterone (nmol/L) |
| Cases                | 833.6 (16.9)     | 632.3 (14.6)   | 21.19 | <0.001    |
| Controls             | 791.5 (16.6)     | 605.4 (14.5)   | 18.23 | <0.001    |
| statistic            | t=0.40           | F=1.63         |    |           |
| p                    | 0.691            | 0.735          |    |           |

3.2 Circadian rhythm of cortisol secretion in depressed cases and depressed controls

As shown in Table 2, there were significant changes in serum cortisol levels during a 24 h cycle for both depressed cases and depressed controls both before and after treatment. The pattern of the changes were, however, somewhat different. Before treatment the normal midnight trough in cortisol levels did not occur: the 00.00 h level was not significantly lower than the 20.00 h value in either the depressed cases \( (F=1.72, p=0.112) \) or in the depressed controls \( (F=1.46, p=0.241) \). However, after six weeks of antidepressant treatment the midnight trough in cortisol reappeared: the 00.00 h level was significantly lower than the 20.00 h value both in the depressed cases \( (F=22.68, p<0.001) \) and in the depressed controls \( (F=15.29, p<0.001) \). For both the cases and controls at each of the five time periods assessed, the post-treatment cortisol values were lower than the pre-treatment cortisol levels, but these differences only reached statistical significance at the 00.00 h time period.

3.3 Comparison of cortisol in depressed cases and depressed controls versus non-depressed controls

The 08.00 h cortisol levels in the 14 depressed cases with prior suicidal behavior before and after treatment (387[11] and 339[12] nmol/L, respectively) were both significantly greater than the level in the 15 non-depressed controls (248[10] nmol/L) (comparison with before-treatment value, \( F=21.43, p<0.001 \)); comparison with after-treatment value, \( F=22.24, p<0.001 \)). However, in the 15 depressed controls the before and after treatment 08.00 h cortisol levels (321[11] and 302[11] nmol/L, respectively) were not significantly different from the level in the non-depressed controls.

Table 2. Circadian rhythm of cortisol secretion in 14 depressed cases with prior suicidal behavior and 15 depressed controls without prior suicidal behavior before and after 6 weeks of treatment with paroxetine (mean [sd], nmol/L)

|                      | 08.00 h | 12.00 h | 16.00 h | 20.00 h | 00.00 h | F         | p         |
|----------------------|---------|---------|---------|---------|---------|-----------|-----------|
| **Depressed cases**  |         |         |         |         |         |           |           |
| before treatment     | 387.6 (10.9) | 297.2 (10.6) | 273.3 (9.7) | 171.6 (9.4) | 154.1 (8.9) | 39.79     | <0.001    |
| after treatment      | 338.6 (11.7) | 190.1 (9.3) | 201.1 (9.6) | 147.4 (9.8) | 91.8 (9.0) | 36.98     | <0.001    |
| **Depressed controls** |        |         |         |         |         |           |           |
| before treatment     | 320.5 (11.1) | 243.3 (10.5) | 231.5 (9.7) | 132.7 (9.1) | 124.3 (8.6) | 38.68     | <0.001    |
| after treatment      | 302.3 (10.8) | 188.5 (9.3) | 192.1 (10.2) | 113.8 (8.9) | 87.1 (8.5) | 34.76     | <0.001    |

**Note:** The table shows the comparison of cortisol levels at different time points before and after treatment for depressed cases and controls, with statistical values indicating whether the differences are statistically significant.
3.4 Comparison of DST results

Eight of the 14 depressed cases (57.1%) had a positive dexamethasone suppression test (i.e., 'non-suppression') but only 3 of the 15 depressed controls (20.0%) had a positive test ($\chi^2=4.24, p=0.039$).

3.5 The correlation between serum cortisol and sex, age, and HAMD scores

The mean (sd) total HAMD scores before and after treatment were 41.6 (7.3) and 21.7 (4.5) for the depressed cases who had had prior suicidal behavior and 39.3 (7.1) and 19.6 (4.2) for the depressed controls who did not have prior suicidal behavior. The differences in mean scores between the groups were not statistically significant either before treatment ($t=0.86, p=0.397$) or after treatment ($t=1.30, p=0.205$). In the depressed cases both at the time of enrollment and after 6 weeks of treatment there was a statistically significant positive correlation between the serum cortisol level and the HAMD total score and between the serum cortisol level and the hopelessness and suicidal ideation item scores of the HAMD. The comparable correlation coefficients in the depressed control subjects were also positive but none of them reached statistical significance.

3.6 Subsequent suicidal behavior in the 6-month follow-up period

During the 6 months of post-treatment follow-up, one of the 14 depressed cases made a suicide attempt and two experienced suicidal ideation while none of the 15 depressed controls reported suicide attempts or ideation. Given the small numbers of subjects involved, this difference was not statistically significant (Fisher's exact test, $p=0.099$).

4. Discussion

4.1 Main findings

These findings confirm previous research about the hyperfunctioning of the HPA axis in persons with depression and the gradual return to normal of HPA functioning as the symptoms of depression subside with treatment.$[8,9,13-17]$ We found elevated serum and urinary cortisol levels, reduction or disappearance of the diurnal fluctuation in serum cortisol levels, non-suppression of cortisol levels with dexamethasone, and a positive correlation between measures of depression severity and serum cortisol.

A few of the results distinguished HPA functioning in depressed patients who did and did not report prior suicidal behavior. Most dramatic was the much higher rate of a positive DST in depressed patients with prior suicidal behavior than in depressed patients who did not have prior suicidal behavior (57% v. 20%), a finding that has been reported by other investigators.$[18]$ And the correlation between measures of serum cortisol and reported hopelessness and suicidal ideation was stronger in depressed patients with prior suicidal behavior than in those without prior suicidal behavior.

4.2 Limitations

The main limitation of the study is that the relatively small sample size and the relatively high dropout rate meant that there were not enough cases in the analysis to adjust for several important confounders. For example, the relationship between HPA axis functioning and depression may vary by age and the relationship between the DST result in depressed subjects with...
suicidal behavior may vary by the time between the last suicidal act and the test, but we could not stratify our analysis to assess these possibilities. Moreover, several of the negative results – such as the lack of a significant difference between the depressed cases and depressed controls – may have been the result of low power to identify significant differences (i.e., Type II errors).

Another difficulty was accurate classification of depressed subjects into those with and without prior suicidal behavior. Patients will often deny prior suicidal behavior and ideation. If the behavior was overt, family informants can usually clarify the situation, but family members are often not aware of patients’ prior suicidal ideation. Because of limited numbers of subjects who reported suicide attempts, we included self-reported suicidal ideation as a ‘suicidal behavior’; this may have diluted the biological purity of the sample and, thus, decreased the distinctiveness of the observed differences between HPA functioning in patients with and without prior suicidal behavior.

We used an 80% drop in cortisol level after administration of dexamethasone as the cut-off for a normal response. It would have also been possible to use a receiver operator curve (ROC) analysis to identify the cut-off point on the DST that best discriminated depressed subjects with and without prior suicidal behavior. ROC analysis could also be employed with other measures, such as the drop in the 00.00 h cortisol level, to identify quantitative measures that best discriminate depressed cases from depressed controls.

We did not conduct a detailed psychiatric examination of the individuals who were selected as non-depressed controls from persons who came to the hospital for a routine physical exam, so it is not possible to definitively rule out depression in these subjects. And the timing of these individuals’ attendance at the wellness clinic at the hospital varied over the daytime working hours (08.00 h to 16.00 h), so it was not possible to do the blood sampling at the same time in all of these control subjects.

4.3 Significance

Our findings add to the growing body of research about the relationship of HPA axis hyperfunctioning to different depressive states and to suicidal behavior. We confirm findings from other countries in a mainland Chinese sample of depressed patients.

The parallel fluctuations in cortisol levels and in the severity of depressive symptoms suggest that HPA axis dysfunction in depression is a state rather than a trait, but it is certainly possible that there is also an underlying proclivity to HPA axis hyperfunctioning in persons prone to depression (that is, a trait).

It remains unclear whether or not specific HPA axis measures will be able to serve as biomarkers for suicide risk in individuals with depression. Many questions remain. Is the HPA axis dysfunction seen in depressed patients with suicidal behavior simply a reflection of a more severe form or depression or are there suicide-specific components that may also be present in individuals with suicidal behavior who do not have depression? Can the identified measures predict suicide in depressed individuals who never had suicidal behavior or are they only useful to predict repeated behavior in individuals who have already made a suicide attempt?

Much larger studies of inception cohorts of depressed patients that track HPA axis functioning over time while monitoring the severity of depressive symptoms, suicidal ideation and suicidal acts will be needed to resolve these issues.

Conflict of interest

The authors report not conflict of interest related to this study.

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抑郁障碍患者下丘脑-垂体-肾上腺轴的功能与自杀行为的关系

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摘要

背景 目前对抑郁障碍患者自杀行为的神经-内分泌研究仍较少，且结果多不一致。

目的 探讨国内抑郁障碍患者下丘脑-垂体-肾上腺（hypothalamus-pituitary-adrenal, HPA）轴释放功能与自杀行为的关系。

方法 比较 14 例 2 个月内有过自杀行为的抑郁障碍患者（抑郁研究组）和 15 例不伴自杀行为的抑郁障碍患者（抑郁对照组）的HPA轴功能。以地塞米松抑制试验（dexamethasone suppression test, DST）、一天中血浆皮质醇浓度的昼夜变化（在帕罗西汀治疗前及治疗 6 周后评估）以及治疗前和治疗后的 24 小时尿 17-羟皮质醇和 24 小时尿游离皮质酮，评估HPA轴释放功能。同时以汉密顿抑郁量表（Hamilton Depression Rating Scale, HAMD）评定抑郁严重程度。另外测定 15 名无抑郁障碍的健康体检者的白天皮质醇浓度。

结果 抑郁研究组与抑郁对照组之间 24 小时尿皮质醇浓度的差异无统计学意义，尿皮质醇浓度差异也无统计学意义。治疗前两组血浆皮质醇的午夜分泌低谷均不明显，而治疗后的分泌低谷变得明显。抑郁研究组 DST 阳性率显著高于对照组（57% 对 20%，χ²=4.24，p=0.039）。无论治疗前后，抑郁研究组患者血浆皮质醇水平与 HAMD 量表总分及绝望感和自杀观念的因子分呈显著正相关，但是抑郁对照组中这些相关系数无统计学意义。抑郁研究组早晨 8 点的血浆皮质醇浓度在治疗前后均显著高于健康对照组，而抑郁对照组的这一浓度并不比健康对照组高。

结论 本研究结果与先前关于抑郁症与 HPA 轴功能关系的研究结果大致相同。尽管如此，有自杀行为与无自杀行为的抑郁症患者之间还是存在某些差异。这些差异提示可能存在着自杀相关的 HPA 轴功能紊乱。有必要在大样本研究中进一步验证这些差异，以期能够在只报告有过自杀观念的人群中鉴别出实际有过自杀行为的个体。