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Plasma concentrations of neurotransmitters and postpartum depression

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ABSTRACT

Objective: To determine associations between postpartum depression (PPD) and plasma neurotransmitters.

Methods: We conducted a case-control study nested to a prospective cohort established in 3 comprehensive tertiary hospitals in Changsha, Hunan, China from February to September 2007. The Chinese version of the Edinburgh Postnatal Depression Scale (EPDS) was used at 2 weeks postpartum to screen PPD, with a score of 13 or higher as the cut-off for PPD. The women with matched age but without PPD and delivery within 5 years were selected as controls. The levels of plasma monoamine neurotransmitters including serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), and norepinephrine (NE), and peptide neurotransmitters including neuropeptide Y (NPY) and substance P (SP) in maternal blood samples taken at 2 weeks postpartum were measured and compared between PPD women ($n=42$) and controls ($n=42$).

Results: Plasma levels of 5-HT and NPY were significantly lower while plasma levels of NE and SP were significantly higher in PPD women than those in the controls. For women with PPD, a negative correlation between NPY and NE ($r=-0.36$, $P<0.05$) was observed.

Conclusion: There are changes in plasma levels of neurotransmitters in women with PPD, and there are potential interactions between different neurotransmitters.

KEY WORDS

postpartum depression; 5-hydroxytryptamine; norepinephrine; neuropeptide Y; substance P

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血浆神经递质浓度与产后抑郁症的关系

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[摘要] 目的: 探讨血浆神经递质与产后抑郁症(postpartum depression, PPD)的关联。方法: 于2007年2至9月在湖南长沙3家三甲医院开展一项前瞻性巢式病例对照研究。运用爱丁堡产后抑郁量表(Edinburgh Postnatal Depression Scale, EPDS)中文版对产后2周产妇进行PPD筛查, 得分 ≥ 13 分者确定为PPD患者($n=42$)。每个PPD患者按1:1抽取正常产妇为对照组($n=42$), 两组按照分娩医院(同一医院)与年龄(± 5 岁)进行匹配。在产后2周抽取血液样本, 比较PPD组和对照组产妇的血浆单胺类递质及肽类神经递质水平, 其中血浆单胺类递质包括5-羟色胺(5-hydroxytryptamine, 5-HT)、多巴胺(dopamine, DA)、去甲肾上腺素(norepinephrine, NE), 肽类神经递质包括神经肽Y(neuropeptide Y, NPY)和P物质(substance P, SP)。结果: PPD组5-HT和NPY血浆水平明显低于对照组, 而NE和SP血浆水平明显高于对照组(均 $P < 0.05$)。PPD组NPY和NE血浆水平之间呈负相关($r = -0.36$, $P < 0.05$)。结论: PPD产妇存在多种神经递质水平的改变, 不同神经递质之间具有潜在相互作用。

[关键词] 产后抑郁症; 5-羟色胺; 去甲肾上腺素; 神经肽Y; P物质

Postpartum depression (PPD), affecting 10%–20% women^[1-5], is a subtype of major depression that occurs within 4 weeks after delivery^[6-7]. The adverse long-term effects of PPD on women, infants, and families are increasingly recognized as a major public health issue. In terms of the biological vulnerability of underlying PPD, the exact mechanism has not been explained. Studies^[3, 8-10] have shown that hormonal fluctuations and interaction in biomarkers of function might be involved in the development of neuropsychiatric disorders or exacerbation of existing disorders in women across menstrual cycle, during pregnancy and postpartum, and during the menopausal transition.

Monoamine neurotransmitters are neurotransmitters and neuromodulators that contain one amino group which is connected to an aromatic ring by a two-carbon chain. All monoamines are derived from aromatic amino acids such as phenylalanine, tyrosine, tryptophan, and the thyroid hormones by the action of aromatic amino acid decarboxylase enzymes. The function of monoamine is not clear but it is thought to trigger crucial components such as emotion, arousal, and cognition. Serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), and norepinephrine (NE) are main monoamine neurotransmitters and they are associated with patients affected by depression but the observed associations varies among studies^[10-12]. Serum and platelet 5-HT levels are

also associated with PPD or postpartum blue^[13-15].

Neuropeptide Y (NPY) is a 36-amino acid neuropeptide that acts as a neurotransmitter in the brain and in the autonomic nervous system of humans beings. Some studies suggest that patients with depression have lower plasma NPY levels than controls^[16-17] and plasma NPY is a marker for resilience^[18] while other studies found no association between serum NPY and depressive disorders, PTSD, and resilience^[19-20]. Substance P (SP) is an 11-residues-neuropeptide that involves in the regulation of numerous biological functions including stress regulation^[21]. SP levels in the cerebrospinal fluid and serum are found to be elevated in patients with major depression, and SP serum levels were decreased in patients treated with the antidepressant^[22-24].

Previous studies on the association between PPD and neurotransmitters have usually examined individual neurotransmitter, with no comprehensive assessment for the association of PPD with different neurotransmitters and their interactions in a single study population simultaneously. This study was attempted to fill this gap in the literature of the science on PPD and neurotransmitters.

I Materials and methods

I.1 Subjects

This was a case control study, nested to a prospective

cohort study conducted in Changsha, Hunan, China, from February to September 2007. We obtained approval from the Research Ethics Board of Central South University prior to the commencement of the study. In the original cohort study, subjects were recruited in Xiangya Hospital and the Third Xiangya Hospital of Central South University, and Hunan Maternal and Infant Hospital, Changsha, Hunan, China, during their prenatal visits at 30 to 32 weeks of gestation. Nulliparous and married women aged 20–45 years presenting in participating hospitals for prenatal care and planning to stay in Changsha city during the postpartum period were recruited. Participants with records of bipolar disorders, schizophrenia or other mental illnesses, major chronic diseases, or obstetric and pregnancy complications (severe preeclampsia/eclampsia, placenta previa, placental abruption, major postpartum infection, still birth, major birth defects, or birth weight of neonate less than 1 500 g) were excluded from the study.

1.2 Ascertainment of PPD

The Chinese version of Edinburgh Postnatal Depression Scale (EPDS)^[25-26] was used at 2 weeks postpartum to assess PPD with a cut-off score over or equal to 13. In Changsha, routine follow-up was scheduled 2 weeks postpartum for all delivering women. Because by definition, PPD has an onset within 4 weeks postpartum, to reduce the burden of participating women, we decided to assess PPD at 2 weeks postpartum, incorporating their routine postpartum follow-up. All participants were Han Chinese in origin. After a complete description of the study, a written informed consent was obtained.

1.3 Serum neurotransmitters and neuropeptides assay

A random sample of women with PPD and matched women without PPD (matched by same delivery hospital and age ± 5 years) was chosen from the participants for laboratory investigation on neurotransmitters. Approximately 3 mL of peripheral blood was drawn via antecubital vein from the participants at two weeks postpartum using EDTA anticoagulant tubes. After thoroughly being mixed, centrifuged 3 000 r/min at 4 °C for 10 minutes, plasma samples were obtained and stored at -70 °C until determination of neurotransmitters. The levels of plasma 5-HT, DA, and NE were measured using high performance liquid chromatography with the electrochemical detection (HPLC-ECD). Plasma levels of NPY and SP were measured using an enzyme-linked

immunosorbent assay (ELISA).

1.4 Statistical analysis

All analyses were performed using SPSS for windows (Version 13.0; SPSS, Chicago, IL, USA). We firstly described demographic and obstetric characteristics between PPD women and controls. Chi-square test was used for categorical variables and *t*-test was used for continuously distributed variables. Secondly, we compared differences of plasma neurotransmitters and neuropeptides levels between PPD women and controls using *t*-test. Thirdly, we analyzed the correlations between EPDS total scores in PPD women and the levels of neurotransmitters and neuropeptides using Pearson correlation analysis. Finally, we analyzed the correlations between plasma levels of monoamine neurotransmitters and levels of neuropeptides using Pearson correlation analysis. $P < 0.05$ was considered statistically significant.

2 Results

A total of 43 PPD women and 43 individually matched controls were selected for laboratory analysis. Our laboratory test for biomarkers was done in 43 samples per batch. To reduce laboratory cost of the study and to maintain a reasonable study power, we used a 1:1 case control ratio with 43 samples per batch. Due to an operating error, a PPD case sample was dropped out. Thus, 42 PPD cases and 42 controls were included in the final analysis of neurotransmitters and neuropeptides.

2.1 Socio-demographic and perinatal characteristics of PPD women and controls

There were significant differences in maternal education and mode of delivery between PPD women and controls, while there were no differences in other variables (Table 1).

2.2 Comparison of plasma levels of neurotransmitters and neuropeptides between PPD women and controls

Plasma levels of 5-HT and NPY were lower in PPD women than those in the controls ($P < 0.05$ or $P < 0.01$), while plasma levels of NE and SP in PPD women were higher than those in the controls ($P < 0.05$). There were no differences in the DA level between PPD women and controls ($P < 0.05$, Table 2).

Table 1 Comparison of socio-demographic and perinatal characteristics between PPD women and controls, Changsha, China, 2007 (n=42)

Characteristics	PPD women	Controls	χ^2 or <i>t</i>	<i>P</i>
Age/year	27.50±3.61	27.62±3.53	0.15	0.88
Education			8.97	0.01
University or higher	6	18		
College	14	7		
High School or lower	22	17		
Income/(Yuan-month ⁻¹)			4.96	0.08
>2 000	14	24		
1 000–2 000	17	12		
<1 000	11	6		
Housing			Fisher's	0.50
Satisfactory	37	38		
Unsatisfactory	5	4		
Planned pregnancy			1.70	0.19
Yes	30	35		
No	12	7		
Gravidity			0.45	0.80
1	17	19		
2	7	8		
≥3	18	15		
Use of pain relief			0.09	0.76
Yes	37	36		
No	5	6		
Mode of delivery			4.94	0.03
Vaginal	4	12		
Caesarean section	38	30		
Birth weight of neonate/g	3 212.38±548.30	3 153.57±455.91	0.53	0.59
Fetal gender			0.21	0.65
Male	26	28		
Female	16	14		

Data of age and birth weight of neonate are presented by $\bar{x}\pm s$ and *t*-test was used.

Table 2 Comparison of plasma levels of neurotransmitters and neuropeptides between PPD women and controls (n=42, $\bar{x}\pm s$)

Groups	5-HT/(ng.mL ⁻¹)	DA/(ng.mL ⁻¹)	NE	NPY/(ng.mL ⁻¹)	SP/(pg.mL ⁻¹)
PPD women	7.21±2.06	3.50±0.80	60.53±10.52	6.14±0.97	884.15±246.78
Controls	8.25±2.24	3.52±1.16	55.04±11.99	6.66±0.79	771.45±267.54
<i>t</i>	2.21	0.13	2.23	2.72	2.01
<i>P</i>	0.03	0.90	0.03	<0.01	0.05

2.3 Correlations between EPDS total score and the plasma levels of neurotransmitters and neuropeptides in PPD women

There was a significantly negative correlation of

EPDS score with 5-HT and NPY ($P<0.05$ or $P<0.01$) and a significantly positive correlation of EPDS score with NE and SP ($P<0.05$ or $P<0.01$, Table 3).

Table 3 Correlation between EPDS total score and plasma levels of neurotransmitters and neuropeptides in PPD women

Variables	<i>r</i>	<i>P</i>
5-HT	-0.41	0.007
DA	-0.14	0.39
NE	0.37	0.02
NPY	-0.36	0.02
SP	0.44	0.003

2.4 Correlations between plasma levels of NPY and monoamine neurotransmitters in PPD women

Plasma level of NPY had significantly negative correlation with NE ($P < 0.05$), while there was no correlation between plasma levels of DA and 5-HT ($P < 0.05$, Table 4).

Table 4 Correlation between plasma levels of NPY and neurotransmitters in PPD women

Variables	<i>r</i>	<i>P</i>
5-HT	-0.18	0.24
DA	-0.05	0.76
NE	-0.36	0.02

2.5 Correlations between plasma levels of SP and monoamine neurotransmitters in PPD women

No significant correlations were observed between plasma levels of SP and neurotransmitters in PPD women (Table 5).

Table 5 Correlation between plasma levels of SP and neurotransmitters in PPD women

Variables	<i>r</i>	<i>P</i>
5-HT	-0.19	0.23
DA	-0.24	0.12
NE	0.07	0.65

3 Discussion

Our case-control study nested to a well-established

cohort of pregnant women in China^[27] found that the plasma level of several neurotransmitters was changed in women who suffered from PPD. In particular, the plasma levels of 5-HT and NPY in PPD women were lower than those in controls but the plasma levels of NE and SP in PPD women were higher than those in controls. Furthermore, for PPD women, a negative correlation between NPY and NE was observed. These findings are in general consistent with recently published data, although discrepancies did occur.

Previous studies^[13-15, 28] found that there is a trend to a decrease of serum 5-HT level in cases of maternal depression, and there is a negative correlation between 5-HT level and EPDS scores. Some authors^[29] assessed platelet serotonin transporter binding in depressed pregnant women, normal healthy pregnant women, depressed postpartum women, and normal healthy postpartum women, and they observed significant differences in the dissociation constant (Kd) of platelet binding sites among the 4 groups, in which PPD women had the highest Kd values. An observation on brain 5-HT_{1A} receptor binding potential in healthy and depressed postpartum women demonstrates that postsynaptic 5-HT_{1A} receptor binding in PPD is reduced 20%–28% relative to controls, with most significant reductions in anterior cingulate and mesiotemporal cortices^[30]. The therapeutic effects of major antidepressants for adult depression are believed to through their ability to increase 5-HT levels and to enhance 5-HT functions^[10], which lead further validity of our finding on lower plasma 5-HT level in patients with PPD.

We found that the plasma level of NE in PPD women was significantly higher than that in controls and EPDS score in PPD women was positively associated with NE. These findings are consistent with literature. A study reported on plasma catecholamine levels in both depression and PPD women show a higher level than those of the controls^[31]. Moreover, noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol level at 6 weeks is found to be increased in women with postpartum blues and is positively correlated to blue score^[13].

In our study samples, plasma NPY level in PPD women was lower but plasma SP level was higher than those in controls. In PPD women, EPDS score was negatively correlated with plasma NPY while positively correlated with SP. Furthermore, a negative correlation between NPY

and NE was observed in PPD women. Human studies^[32] on the role of NPY in major adult depression and mood disorders have yielded conflicting results. For example, compared with healthy individuals, Irwin et al^[33] found an increase but Hashimoto et al^[16] found a decreased plasma NPY levels in depressed patients, while other studies^[19-20] found no differences in the serum NPY levels between the two groups. On the other hand, findings on the association between cerebrospinal fluid NPY levels and depression are consistent. For example, Hou et al^[17] reported that cerebrospinal fluid NPY levels are reduced in the first episode in patients with depression and Nikisch et al^[34] reported that antidepressants increase NPY in cerebrospinal fluid. Kormos et al^[35] reviewed that serum and cerebrospinal fluid SP levels are elevated in patients suffering from major adult depression. Moreover, after antidepressant treatment responders showed a reduction in SP serum levels^[22, 24]. NPY is colocalized with various classical neurotransmitters including NE centrally, and with catecholamines in the adrenal medulla. Diminished NPY transmission therefore can lead to the increased corticotropin-releasing factor, generating neuroendocrine, autonomic, and behavioral manifestations of anxiety and depression^[36]. NPY administered into the basolateral nucleus of the amygdala could produce long lasting stress resilient behavior (8 weeks after injection), without noticeable alterations in the hypothalamic-pituitary-adrenal (HPA) axis^[37]. The importance of NPY in resilience has also been captured in the studies^[18] of patients with post-traumatic stress disorder in which levels of NPY are found to be significantly correlated with symptom improvement and positive coping. Similar correlations are found between performance and NPY in special-forces soldiers during training^[38]. Thus, NPY plays an important role in regulating resilience. The effect of NPY in mediating resilience in humans is corroborated in animal studies^[37, 39]. Moreover, 5-HT has reciprocal influences with NPY and can impact the antidepressant properties of NPY^[40]. However, we did not find a correlation between 5-HT and NPY in PPD women, may be owing to limited sample size in our study.

Besides, we did not find an association between PPD and DA. In the literature some authors^[11] reported that the increased DA transporter levels and decreased dopamine levels could play an important role in the pathophysiology of major adult depression. They established the depressive

symptoms subscale of the profile of mood states in healthy subjects with and without depression, and used Single-photon Emission Computed Tomography (SPECT) imaging to determine selective DA transporter brain imaging in the basal ganglia. They found an increased DA transporter binding, especially in the right caudate nucleus in subjects with depression, and this increase is correlated with decreased DA levels in the right caudate nucleus^[11]. For the very few studies that examined the association between PPD and DA, the results are inconsistent. Some authors^[41] reported that plasma DA levels in PPD women are significantly lower than those in the controls, and are negatively correlated with EPDS score. Others^[14] observed an opposite result: Plasma DA levels in PPD cases are significantly higher than those in healthy subjects, and are positively correlated with EPDS score. There is no difference in the plasma DA level between depression women and control^[31]. On the other hand, the DA plasma level in PPD group is higher than that in the prenatal group, depression group, and control group^[31]. The authors^[31] suggested that estrogen and progesterone levels decline rapidly in postpartum, reducing the recycling role of monoamine neurotransmitters in the hypothalamus, and then affecting the release transmission of DA in the central nervous system, which finally lead to the onset of PPD.

Our case-control study showed that plasma levels of 5-HT and NPY are significantly lower while plasma levels of NE and SP are higher in women affected by PPD than those in normal women. Furthermore, we found a negative correlation between NPY and NE in PPD women. These findings suggest that the roles of monoamine neurotransmitters and neuropeptides and their interaction in the development of PPD may be similar to the effects of clinical depression unrelated to childbirth.

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