Clinica Chimica Acta 464 (2017) 142–147

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Decreased plasma concentrations of brain-derived neurotrophic factor in preeclampsia

Luiza Oliveira Perucci [a,b], Érica Leandro Marciano Vieira [c], Antônio Lúcio Teixeira [c], Karina Braga Gomes [a,b], Luci Maria Dusse [a,b], Lirlândia Pires Sousa [a,b,*]

[a] Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[b] Programa de Pós-Graduação em Análises Clínicas e Toxicológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[c] Laboratório Interdisciplinar de Investigação Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

ARTICLE INFO

Article history:
Received 27 September 2016
Received in revised form 21 November 2016
Accepted 21 November 2016
Available online 22 November 2016

Keywords:
Brain-derived neurotrophic factor
Annexin A1
Preeclampsia

ABSTRACT

Background: Preeclampsia (PE) is a disease characterized by excessive maternal inflammatory response. Early studies suggested that brain-derived neurotrophic factor (BDNF) modulates inflammation. The main objective of this study was to investigate BDNF plasma concentrations in PE women and to compare with BDNF concentrations from normotensive pregnant women. We also investigated the association among the plasma concentrations of BDNF and inflammatory mediators, and maternal clinical features.
Methods: BDNF plasma concentrations were measured by ELISA in 38 PE women (17 early onset and 21 late onset) and in 20 normotensive pregnant women (Norm) matched for gestational age (Norm < 34 weeks: $n = 8$; Norm ≥ 34 weeks: $n = 12$). Correlation analyses between laboratory parameters and clinical characteristics were evaluated through Spearman's coefficients.
Results: BDNF concentration was lower in PE women than in normotensive pregnant women, but no difference was detected between the subgroups of PE women and normotensive pregnant women. BDNF correlated negatively with annexin A1, and positively with body mass index and diastolic blood pressure. No correlation was significant in normotensive pregnant women.
Conclusions: Lower BDNF plasma concentrations and cross-talk between BDNF and AnxA1 signaling pathways might be involved in PE pathogenesis.

1. Introduction

Preeclampsia (PE) is a hypertensive and multi-system disease of pregnancy that represents one of the leading causes of maternal and fetal morbidity/mortality worldwide [1]. Although its pathophysiology is not fully elucidated, a series of evidence suggests that defective placentation is the initiating event which contributes to systemic endothelial dysfunction, oxidative stress and inflammation [2]. PE can be classified according to the gestational age (GA) of clinical symptoms development in early onset (GA < 34 weeks) and late onset (GA ≥ 34 weeks) [3].

Brain-derived neurotrophic factor (BDNF) is a growth factor that belongs to the neurotrophin family, and is abundantly expressed in the central and peripheral nervous systems. BDNF signals through tyrosine kinase B (TrkB) receptor to regulate neuronal development, function and plasticity [4]. BDNF is also expressed in non-neuronal tissues [5]. In addition to neuroprotective effects, BDNF stimulates angiogenesis, placental development and fetal growth [6,7]. It has also been shown that BDNF expression is modulated by oxidative stress and inflammation [8,9]. Conversely, BDNF is able to modulate inflammatory responses [10–12]. Therefore, altered concentrations of BDNF could contribute to PE pathogenesis.

Previous studies that evaluated BDNF circulating concentrations in PE women have reported either lower, higher or similar concentrations when compared with normotensive pregnant women [13–16]. We aimed to investigate BDNF plasma concentrations in women with early onset PE and late onset PE and in normotensive pregnant women matched for gestational age and socioeconomic background. We also analyzed the relationship among the concentration of BDNF, inflammatory molecules (soluble tumor necrosis factor receptor-1 - sTNF-R1 and annexin A1 - AnxA1) evaluated in previous studies [17,18] and maternal clinical features in order to better understand the role of BDNF in PE pathogenesis.

Abbreviations: AnxA1, annexin A1; BDNF, brain-derived neurotrophic factor; DBP, diastolic blood pressure; GA, gestational age; GWG, gestational weight gain; Norm, normotensive pregnant women; PE, preeclampsia/preeclamptic; SBP, systolic blood pressure; sTNF-R1, soluble tumor necrosis factor receptor-1; TNF-α, tumor necrosis factor alpha; TrkB, tyrosine kinase B.

* Corresponding author at: Av. Antonio Carlos, 6627 - Pampulha, 31270-901 Belo Horizonte, Minas Gerais, Brazil.
E-mail address: lipsousa72@gmail.com (L.P. Sousa).

http://dx.doi.org/10.1016/j.cca.2016.11.034
0009-8981/

2. Materials and methods

2.1. Ethics

The procedures in this study were in accordance with Ethics Committees of Universidade Federal de Minas Gerais and the participating hospitals (Santa Casa de Misericórdia de Belo Horizonte: Fundação Hospitalar do Estado de Minas Gerais; Hospital Municipal Odilon Behrens), and a written informed consent was obtained from each participant.

2.2. Patients

This study included 38 PE women and 20 normotensive pregnant women in the third trimester of pregnancy who were recruited from Brazilian public hospitals. PE women were stratified in early onset PE ($n = 17$) and in late onset PE ($n = 21$) subgroups [3]. Normotensive pregnant women were stratified in 2 subgroups considering the cut-off of 34 weeks (Norm < 34 weeks: $n = 8$; Norm ≥ 34 weeks: $n = 12$) to match the subgroups of PE women.

PE was defined by systolic and diastolic blood pressure ≥ 140/90-mm Hg after 20 weeks of gestation in a previously normotensive women, confirmed by 2 consecutive readings at least 4 h apart in association with proteinuria (≥300 mg/24 h or ≥1 + reading on dipstick in a random urine specimen) and/or evidence of end-organ dysfunction (thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual disturbances) [1]. Normotensive pregnant women had blood pressure < 120/80 mm Hg and no history of hypertension. All women were matched according to socioeconomic status. The exclusion criteria for both groups were: chronic hypertension, obesity (grades II and III) [19], diabetes, cancer, homeostatic abnormalities, infectious, cardiovascular, autoimmune, renal, hepatic, psychiatric and neurological diseases.

2.3. Sample collection, processing and storing

Five milliliters of maternal venous blood were collected in EDTA anticoagulant-coated tubes (BD Vacutainer). The blood was centrifuged at 3000*g* for 15 min at room temperature to separate the plasma. The plasma aliquots were stored at −80 °C until analyses.

2.4. BDNF measurement

BDNF plasma concentrations were measured by ELISA using a commercial available kit (R&D Systems) according to the manufacturer's instructions and were reported as pg/ml. The BDNF antibody used in this assay detects human BDNF in ELISA, and no cross-reactivity or interference was observed with recombinant human glial cell-derived neurotrophic factor, β-nerve growth factor, neurotrofin 3 or neurotrofin 4.

2.5. Statistical analysis

The data were analyzed using SPSS software ver 19.0. The normality of continuous variables was assessed using Shapiro-Wilk's W-test. Continuous variables not normally distributed were analyzed by Kruskal-Wallis test. When differences were detected among the groups, they were compared 2 × 2 with the Mann-Whitney *U* test or Mann-Whitney *U* test followed by Bonferroni's correction (4 groups). The comparison of continuous variables with normal distribution was performed by analysis of variance (ANOVA) test with *post hoc* LSD test (4 groups) or Student's *t*-test (2 groups). The comparison of categorical variables was performed by Pearson χ^2 test. Parametric data were expressed as mean ± SD, non-parametric data as median (25th–75th percentiles) and categorical variables as absolute number (percentage). Spearman's correlation coefficients (r_s) were used to investigate the possible correlations among the plasma concentrations of BDNF and inflammatory mediators evaluated in previous studies [17,18], and clinical parameters in PE women and in normotensive pregnant women. A *P*-value <0.05 denoted statistical significance.

3. Results

3.1. Clinical characteristics

Table 1 shows the clinical characteristics of the studied groups. No significant difference was detected in age, body mass index (BMI) before pregnancy, gestational weight gain (GWG) and GA at blood collection between normotensive pregnant women and PE women. PE group had lower number of gestations ($P = 0.009$) and higher number of primiparas ($P = 0.013$) than normotensive group. As expected, systolic and diastolic blood pressures (SBP and DBP, respectively) were significantly increased in PE women (all $P < 0.001$). There was no significant difference in educational degree between the groups.

The clinical characteristics of the subgroups of normotensive pregnant women and PE women are displayed in Table 2. No differences were found for age, BMI before pregnancy, number of gestations, number of primiparas and educational degree among the subgroups. Pregnant women with late onset PE had higher GWG than normotensive pregnant women with GA < 34 weeks ($P = 0.004$). As expected, GA at blood collection was higher in late onset PE when compared with early onset PE and normotensive pregnant women with GA < 34 weeks, and in normotensive pregnant women with GA ≥ 34 weeks when compared with early onset PE and normotensive pregnant women with GA < 34 weeks (all $P < 0.001$). In addition, SBP and DBP were higher in early onset PE and late onset PE when compared with normotensive pregnant women with GA < 34 weeks and normotensive pregnant women with GA ≥ 34 weeks (all $P < 0.001$). No participant in this study was illiterate or had completed higher education.

3.2. BDNF plasma concentrations

BDNF plasma concentrations were lower in PE women [2970 (2021–5403) pg/ml] than in normotensive pregnant women [4913 (2548–9551) pg/ml] ($P = 0.029$) (Fig. 1). No significant difference was

Table 1
Clinical characteristics of normotensive pregnant women and PE women.

Variables	Norm ($n = 20$)	PE ($n = 38$)	*P*
Age (y)[a]	23 (19–27)	26 (21–29)	0.325
BMI (kg/m^2)[b]	22.4 ± 3.5	23.5 ± 2.9	0.872
GWG (kg)[a]	10.4 (8.5–12.7)	12.5 (9.3–18.7)	0.062
GA (weeks)[a]	35 (30–39)	34 (32–38)	0.658
Parity			
Gravidity (n)[a]	2 (1–3)	1 (1–2)	0.009
Primiparas (%)[c]	5 (25)	23 (61)	0.013*
SBP (mm Hg)[a]	110 (100−110)	160 (150–170)	<0.001***
DBP (mm Hg)[a]	70 (70–70)	102 (100−111)	<0.001***
Education[c]			0.094++
Informed (%)	20 (100)	28 (74)	
Elementary school (%)+	1 (5)	4 (14)	
Middle school (%)+	11 (55)	7 (25)	
High school (%)+	8 (40)	17 (61)	
Not informed (%)	0 (0)	10 (26)	

Abbreviations: BMO before pregnancy; GWG, gestational weight gain; GA, gestational age at blood collection; n, number/sample size; SBP, systolic blood pressure; DBP, diastolic blood pressure; Norm, normotensive pregnant women; PE, preeclamptic women.
[a] Mann-Whitney *U* test; data are presented as median (25th–75th percentiles).
[b] Student's *t*-test; data are presented as mean ± SD.
[c] Pearson χ^2 test; data are presented as number (percentage).
* $P < 0.05$.
*** $P < 0.001$.
+ The percentage of each educational variable was calculated considering the total of patients who informed their educational degree in each group.
++ The analysis of education considered only patients who informed their educational degree.