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Short communication

Maternal serum ratio of ghrelin to obestatin decreased in preeclampsia

Weiguang Wu [a], Xiaobin Fan [b,*], Yuecheng Yu [c], Yingchun Wang [a]

[a] Department of Obstetrics & Gynecology, Affiliated Hospital, Logistical College of Chinese People's Armed Police Forces, Tianjin 300162, PR China
[b] Maternity & Children Hospital of Northwest District, Shaanxi, Xi'an 710003, PR China
[c] Department of Obstetrics & Gynecology, Xijing Hospital, Fourth Military Medical University, Shaanxi, Xi'an 710033, PR China

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ABSTRACT

Objective: Ghrelin, an endogenous for the growth hormone secretagogue receptor, has been shown to participate in blood pressure regulation. Obestatin, encoded by the same gene as ghrelin, is described as a physiological opponent of ghrelin. We hypothesized that ghrelin/obestatin imbalance played a role in the pathogenesis. This study was designed to determine the alterations of ghrelin and obestatin concentrations and ghrelin/obestatin ratio in maternal serum in preeclampsia.
Method: This retrospective case–control study included 31 preeclampsia and 31 gestational week-matched normal pregnancies. Ghrelin and obestatin concentrations in maternal serum were determined by radioimmunoassay, and the ghrelin/obestatin ratio was calculated.
Results: The ghrelin concentration and ghrelin/obestatin ratio in maternal serum were significantly lower in preeclampsia than in normal pregnancies (214.34 ± 14.27 pg/mL vs 251.49 ± 16.15 pg/mL, $P = 0.041$, 1.07 ± 0.09 vs 0.82 ± 0.08, $P = 0.023$). The obestatin concentration in maternal serum was significantly higher in preeclampsia than in normal pregnancies (276.35 ± 15.38 pg/mL vs 223.53 ± 18.61 pg/mL, $P = 0.019$). The systolic blood pressure in preeclampsia was negatively correlated with ghrelin concentration and ghrelin/obestatin ratio ($r = -0.549$, $P = 0.003$; $r = -0.491$, $P = 0.004$) and was positively correlated with obestatin concentrations in preeclampsia ($r = 0.388$, $P = 0.013$).
Conclusions: The findings of this study suggested disturbance of ghrelin and obestatin in maternal serum in preeclampsia, and ghrelin/obestatin imbalance might play a role in the pathogenesis of preeclampsia.

1. Introduction

Preeclampsia affects approximately 3–5% of all pregnancies worldwide and is a major contributor to maternal morbidity and mortality [1]. This complication is clinically characterized by hypertension, proteinuria, and an exaggerated maternal systemic inflammatory response after 20 weeks of gestation. Although increasing biochemical evidence suggests that the pathophysiological changes in trophoblast cell in the placental bed and the failed conversion of maternal endometrial spiral arteries may be leading causes in the pathogenesis of preeclampsia [2], the underlying etiology of preeclampsia remains unclear.

Ghrelin and obestatin are two gastric mucosa-derived peptides, which have opposing roles in the control of appetite [3]. Given that the receptors of these peptides are located throughout the body, the role of these peptides in body metabolism extends beyond the regulation of only gastrointestinal function. These peptides may play a more active role in the entire body metabolism, appetite regulation, and fuel preference than is currently appreciated. Ghrelin might also play a role in blood pressure regulation in human and in rats [4,5]. Women with pregnancy-induced hypertension have significantly lower levels of ghrelin than normal pregnant women, and a negative correlation exists between plasma ghrelin concentration and systemic blood pressure in normal pregnant women or women with pregnancy-induced hypertension [6,7]. Obestatin, encoded by the same gene as ghrelin, has also been found to play a role in the regulation of blood pressure in humans [8,9]. These results suggest that ghrelin and obestatin together have role in cardiovascular control in pathophysiologic conditions, such as pregnancy-induced hypertension. Considering that some actions of ghrelin oppose those of obestatin, the ghrelin/obestatin ratio may play a critical role in the overall physiological effect and may be a more informative marker than obestatin or ghrelin alone. The ghrelin/obestatin ratio is an alteration in a number of diseases [10,11], thereby indicating that ghrelin/obestatin imbalance may play a role in the pathogenesis of these diseases.

* Corresponding author.
E-mail address: xbfan@126.com (X. Fan).

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In this study, we investigated the alterations of ghrelin and obestatin levels and the ghrelin/obestatin ratio in maternal serum in preeclampsia, as well as explored their relationships with blood pressure. We hypothesize that ghrelin/obestatin imbalance play a role in the pathogenesis of preeclampsia.

2. Materials and methods

2.1. Study population

In this retrospective case–control study, 62 pregnancies (31 pregnancies with preeclampsia and 31 gestational week-matched pregnancies with no complication) were undertaken. All pregnant women were singleton pregnancies (20–38 weeks of gestation) and were enrolled in the study following a written informed consent at the Obstetrics and Gynecology Department of Affiliated Hospital of Logistical College of Chinese People's Armed Police Force between January 2010 and December 2013. Ethics approval was granted by the Research Ethics Board of Logistical College of Chinese People's Armed Police Force.

Preeclampsia was diagnosed according to the definition of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000) that systolic blood pressure (SBP) was greater than or equal to 140 mmHg and/or diastolic blood pressure (DBP) was greater than or equal to 90 mmHg on two or more measurements at least 6 h apart and proteinuria greater than 0.3 g/24 h. Exclusion criteria for all women included pre-existing hypertension treated with antihypertensive drugs, diabetes mellitus, gestational diabetes mellitus needing insulin treatment, renal disease, liver diseases, heart disease, and hematic disease.

Venous blood samples of pregnant women in 20–38 weeks of gestation were collected from the antecubital vein in the morning between 7:00 and 8:00 after an overnight fast because plasma ghrelin and obestatin levels have been shown to be altered by food intake. The blood samples were immediately transferred into plastic tubes containing ethylenediaminetetraacetic acid-2Na (1 mg/mL) and aprotinin (Phoenix Pharmaceuticals, Belmont, CA; 100 μL containing 0.6 trypsin inhibitor units per milliliter of blood) and centrifuged at 4 °C, 1600*g*, for 15 min. All serum samples were kept at −80 °C prior to assay.

2.2. Ghrelin and obestatin assays

Serum obestatin concentrations were measured after extraction in the reverse phase C18 columns (Phoenix Pharmaceuticals) with a commercial radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals) by using ^{125}I-labeled obestatin as tracer and polyclonal antibody raised in rabbits against human obestatin. Intraassay and interassay coefficients of variation (CV) were less than 5% and 12%, respectively, according to the manufacture. Serum ghrelin concentrations were measured using a commercial RIA kit (Phoenix Pharmaceuticals) with ^{125}I-labeled bioactive ghrelin as a tracer molecule and a rabbit polyclonal antibody against full-length octanoylated human ghrelin. This assay recognized both acylated and des-acylated forms of ghrelin. The intraassay CV was less than 4%, and the interassay CV was less than 8% according to the manufacture.

2.3. Statistical analysis

The data fit a normal distribution by *k*-s test ($P > 0.05$). Data are presented as mean ± standard deviation. Unpaired *t*-test was used to compare parametric variables. Spearman's correlation coefficient was calculated to investigate the association among ghrelin, obestatin, ghrelin/obestatin ratio, and blood pressure in preeclampsia. $P < 0.05$ was considered significant for all statistical analyses. All analyses were performed using SPSS for windows (version 10.0; SPSS Inc., Chicago, IL).

3. Results

3.1. Subject characteristics

The main clinical characteristics of the study population are summarized in Table 1. No significant differences were found in age, gestation week, body mass index, birth weight and smoking between women with preeclampsia and normal pregnancies ($P > 0.05$).

3.2. Differences in ghrelin and obestatin levels in maternal serum

The ghrelin concentrations in maternal serum were 214.34 ± 14.27 pg/mL and 251.49 ± 16.15 pg/mL in women with preeclampsia and normal pregnancies, respectively. The ghrelin concentration in women with preeclampsia was significantly lower than that in women with normal pregnancies ($P < 0.05$) (Fig. 1A). The obestatin concentrations in maternal serum were 276.35 ± 15.38 pg/mL and 223.53 ± 18.61 pg/mL in women with preeclampsia and normal pregnancies, respectively. The obestatin concentration in women with preeclampsia was significantly higher than that in women with normal pregnancies ($P < 0.05$) (Fig. 1B). The ghrelin/obestatin ratios in maternal serum were 1.07 ± 0.09 and 0.82 ± 0.08 in women with preeclampsia and normal pregnancies, respectively. The ghrelin/obestatin ratio in women with preeclampsia was significantly lower than that in women with normal pregnancies ($P < 0.05$) (Fig. 1C).

3.3. Correlations of ghrelin, obestatin, and ghrelin/obestatin ratio with blood pressure

Ghrelin concentration was negatively correlated with SBP in women with preeclampsia ($r = -0.549$, $P = 0.003$), but no correlation was found between ghrelin concentration and DBP in women with preeclampsia ($r = -0.240$, $P = 0.237$). The obestatin concentration was positively correlated with SBP in women with preeclampsia ($r = 0.388$, $P = 0.013$), but no correlation was found between obestatin concentration and DBP in women with preeclampsia ($r = 0.077$, $P = 0.493$). The ghrelin/obestatin ratio was negatively correlated with SBP in women with preeclampsia ($r = -0.491$, $P = 0.004$), but no correlation was found between ghrelin/obestatin

Table 1
The main clinical characteristics of the study population.

Parameters	Preeclampsia ($n = 31$)	Normal pregnancies ($n = 31$)	*P* value
Maternal age (years)	28.46 ± 2.74	29.97 ± 2.98	0.553
BMI (kg/m^2)	22.38 ± 1.59	21.62 ± 1.27	0.555
Gestational week	30.12 ± 1.57	29.19 ± 1.63	0.516
Smoking	2 (2/31)	3 (3/31)	0.846
SBP (mmHg)	153.26 ± 5.97	114.18 ± 6.89	0.001
DBP (mmHg)	101.49 ± 4.12	73.65 ± 4.27	0.001
Proteinuria (g/24 h)	2.31 ± 0.25	0	
Birth weight (kg)	3089.57 ± 17.12	3120.21 ± 15.67	0.4227

Data are mean ± SE.