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Association between circulating levels of galanin and pre-pregnancy body mass index in patients with gestational diabetes mellitus

Zhenwen Zhang [a,b,1], Penghua Fang [b,1], Mingyi Shi [b], Chunmei Gu [c], Yan Wang [a], Ping Bo [b,*], Yan Zhu [a,*]

[a] Department of Endocrinology, Clinical Medical College, Yangzhou University, Yangzhou, Jiangsu, China 225001
[b] Research Institution of Combining Chinese Traditional and Western Medicine, Medical College, Yangzhou University, Yangzhou, Jiangsu, China 225001
[c] Department of Gynaecology and Obstetrics, Yangzhou Maternal and Child Health Care Hospital, Yangzhou, Jiangsu, China 225001

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ABSTRACT

Galanin is an important neuropeptide which induces an increase in obesity and appetite, improving insulin sensitivity and glucose tolerance in experimental animals. Although significantly higher levels of plasma galanin are found in pregnant women with gestational diabetes mellitus (GDM), there is a limited understanding of its precise mechanism underlying this variation. In the present study, concentrations of circulating galanin were determined at baseline in pregnant women with GDM and pregnant women with normal glucose tolerance (NGT). Correlation analyses were performed between galanin and pre-gestational body weight, pre-gestational BMI, and hormone involved in various homeostatic processes. Results showed that plasma galanin level was significantly higher in the patients with GDM than in the NGT subjects ($p < 0.001$). Plasma galanin was positively correlated with pre-gestational body weight ($r = 0.42$, $p = 0.037$), pre-gestational BMI ($r = 0.643$, $p = 0.001$), and fasting blood glucose ($r = 0.840$, $p < 0.001$) in the GDM group. Moreover, a significant negative correlation was shown between galanin and sex hormone binding globulin (SHBG) ($r = -0.901$, $p < 0.001$) in the GDM group. These data indicate that serum galanin concentration increases markedly in pregnant women with GDM, and this increase seems to be related to the increase of pre-gestational BMI and significantly lower SHBG in patients with GDM. Thus, circulating galanin is affected under conditions of altered pre-gestational BMI with highest levels in GDM patients. The increase of galanin under conditions of GDM may indicate a physiological function to improve glucose tolerance which is often impaired in GDM subjects.

1. Introduction

Food intake and body weight are regulated by a complex network of peptide and protein hormones stimulating or inhibiting food intake. Interestingly, galanin, a 30-amino-acid peptide, is the only known peripherally and centrally acting hormone that stimulates food intake and increases body weight. It is synthesized in the central and peripheral nervous system to modulate food intake and energy metabolism (Fang et al., 2012; Fang et al., 2013a; Fang et al., 2013b; Fang et al., 2014a; Fang et al., 2014b). During glucose tolerance tests, galanin gene-knockout mice experienced impaired glucose disposal caused by a reduction in insulin response and insulin-independent glucose elimination (Ahrén et al., 2004), whereas the obese phenotype of the homozygous galanin transgenic C57BL/6 J mice showed an increase in the metabolic rates of lipid and carbohydrate (Poritsanos et al., 2009). A lot of clinical studies have shown that higher level of plasma galanin was found in patients with obesity, type 2 diabetes, and gestational diabetes mellitus (GDM) (Fang et al., 2012; Fang et al., 2013a; Fang et al., 2013b; Legakis et al., 2005). Hyperglycemia or abdominal obesity increases galanin production, which may contribute to insulin resistance and type 2 diabetes (Baranowska et al., 2000; Legakis et al., 2005). During a glucose tolerance test, galanin secretion is positively correlative with the blood glucose level in healthy volunteers, patients with type 2 diabetes, and pregnant women with gestational diabetes mellitus under fasting states (Fang et al., 2013a; Fang et al., 2013b; Legakis et al., 2005; Legalkis et al., 2007). Finally, galanin itself may have a central or permissive role in the pathogenesis of insulin resistance and type 2 diabetes by increasing the glucose uptake of skeletal muscle and adipose tissues (Bu et al., 2013; He et al., 2011; Liang et al., 2012; Zhang et al., 2012), consequently improving insulin sensitivity. Therefore, these studies provide convincing evidence that galanin is an important hormone to elevate energy metabolism and to promote glucose transportations in humans and animals.

GDM is defined as a glucose intolerance of varying severity with onset or first recognition during pregnancy (Petry, 2010). The underlying etiology of GDM appears to be similar to the physiological abnormalities,

* Corresponding authors at: Department of Endocrinology, Clinical Medical College, Yangzhou University, Yangzhou, Jiangsu Province, China. Tel./fax: +86 514 87373195.
E-mail addresses: yzcmed@sina.com, yzzzw@medmail.com.cn (Y. Zhu).
[1] The authors contributed equally to this work.

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including an increase in food intake and body weight as well as a progressive increase in glucose and insulin resistance (Ben-Haroush, Yogev, & Hod, 2004). Although the high circulating level of galanin was observed in patients with GDM in our previous study, there is a limited understanding of its precise mechanism underlying this variation. Thus, the present study aims to evaluate the relationship between plasma galanin and pre-gestational body weight, pre-gestational body mass index (BMI), and hormone involved in various homeostatic processes in pregnant women with GDM.

2. Materials and methods

The present study was conducted in the Clinical Medical College, Yangzhou University, after the approval of the ethics committee dated February 2013. The present study consisted of 25 women at 24–28 weeks of gestation with GDM and 25 women at 24–28 weeks of gestation with normal glucose tolerance (NGT). And all subjects were not previously diagnosed with overt diabetes and without a family history of diabetes. Women with preeclampsia and other pregnancy complications (except GDM) were excluded from the study. Written consents of all participants were obtained and the protocol of the study was approved by the local ethics committee (Clinical Medical College, Yangzhou University).

According to the International Association of Diabetes and Pregnancy Study Groups criteria, one-step method has been employed to diagnose whether or not it is GDM (IADPSG et al., 2010). All subjects were asked to fast for 12 h before blood sampling, which was done between 8:00 and 10:00 a.m. In short, all subjects were given 75 g oral glucose tolerance test (OGTT) at 8:00 a.m. The blood glucose were measured at fasting, 1 and 2 h. The diagnosis of GDM is made when any of the following plasma glucose values are exceeded (fasting blood glucose threshold of 5.1 mmol/L, 1 h blood glucose threshold of 10.0 mmol/L, and 2 h blood glucose threshold of 8.5 mmol/L). Fasting venous blood samples were collected from all cases in the study in the first visit (upon diagnosis) in order to determine levels of galanin, SHBG, glucose, fasting plasma insulin, HbA1c. The blood samples (4 mL) were collected in prechilled EDTA tubes containing aprotinin and were immediately centrifuged for 15 minutes at 1000 × *g* at 4 °C (Fang et al., 2013a; Fang et al., 2013b). Plasma was separated into vials and stored at −80 °C until measurement.

For each case, BMI was calculated at the time of blood collection as weight in kilograms divided by height in meters squared. HbA1c was evaluated by a high performance liquid chromatography technique. Plasma glucose concentrations were measured using oxidase method. Plasma insulin levels were measured by radioimmunoassay. HOMA-IR index was calculated for each patient using the formula [fasting glucose (mmol/L) × fasting insulin (μIU/mL)/22.5].

3. Measurement of SHBG and galanin

SHBG was analyzed by an enzyme-linked immunosorbent assay (Beckmancoulte, Inc. USA). According to the manufacturer's specification, the range of the assay was 0.7–30 nmol/L. Besides, galanin was analyzed by an enzyme-linked immunosorbent assay (USCN Life Science, Inc. Wuhan, China). According to the manufacturer's specification, the range of the assay was 12.35–1000 pg/mL, and the average sensitivity was 4.21 pg/mL. All measurements were performed in duplicate, and the mean of the two measurements was considered. Lastly, the possible correlations between galanin and pre-gestational body weight, pre-gestational BMI, biochemical parameters, and SHBG involved in various homeostatic processes were assessed.

4. Statistical analysis

Data for each respective study were presented as mean ± SD. The differences between the groups were analyzed with independent t-test. Possible correlations between parameters were evaluated by Spearman's correlation coefficient analyses. Statistical significance was considered to be $p < 0.05$. All statistical analyses were performed with SPSS 17.0 for Windows (SPSS, Chicago, IL).

5. Results

The results showed no significant differences in age, gestational weeks, and 1-h insulin between the pregnant women with GDM and NGT, whereas pre-gestational body weight, pre-gestational BMI, fasting glucose, 1-h glucose, 2-h glucose, fasting insulin, 2-h insulin, HbA1c, and HOMA-IR were significantly higher in the pregnant women with GDM compared with NGT (see Table 1). Furthermore, the statistically significant higher level of galanin was found in pregnant women with GDM compared with NGT (26.00 ± 3.31 pg/mL vs. 19.12 ± 2.98 pg/mL, $p < 0.001$), while lower level of SHBG was found in pregnant women with GDM compared with NGT (25.92 ± 4.48 nmol/L vs. 45.67 ± 11.93 nmol/L, $p < 0.001$).

In the present study, galanin exhibited a statistically significant positive correlative relationship with pre-pregnancy body weight ($r = 0.42$, $p = 0.037$) and pre-pregnancy BMI ($r = 0.643$, $p = 0.001$) in the GDM group (see Fig. 1). Besides, a significant positive correlation was shown between galanin and fasting blood glucose ($r = 0.840$, $p < 0.001$) and HOMA-IR ($r = 0.549$, $p = 0.004$) in pregnant women with GDM, although there was no association between galanin and age ($r = 0.257$, $p = 0.216$), gestational weeks ($r = 0.295$, $p = 0.153$), HbA1c ($r = -0.027$, $p = 0.896$), 1-h glucose($r = 0.297$, $p = 0.150$), 2-h glucose ($r = 0.108$, $p = 0.608$), fasting insulin ($r = 0.097$, $p = 0.645$), 1-h insulin ($r = 0.056$, $p = 0.790$), and 2-h insulin ($r = 0.107$, $p = 0.612$) in the same group.

In addition, there were no significant correlations between SHBG and any of the anthropometric or metabolic parameters studied in GDM group except of BMI ($r = -0.547$, $p = 0.005$), fasting blood glucose ($r = -0.808$, $p < 0.001$), and HOMA-IR ($r = -0.533$, $p = 0.006$). Interestingly, a significant negative correlation was shown between galanin and SHBG ($r = -0.901$, $p < 0.001$) in pregnant women with GDM (see Fig. 1).

6. Discussion

Most previous studies suggested that galanin is an important hormone to regulate energy metabolism and homeostasis (Fang et al., 2012; Legakis et al., 2005). A significantly higher level of plasma galanin was found in patients with GDM in our previous study (Fang et al., 2013a; Fang et al., 2013b). However, there is a limited understanding of its precise mechanism underlying this variation.

BMI and obesity are strong predictors of risk of developing insulin resistance and diabetes mellitus. A wealth of evidences now support that galanin stimulates feeding behavior and body weight as well as

Table 1
Biochemical and demographic characteristics of two groups.

	NGT	GDM	p value
N	25	25	
Age (years)	25.20 ± 1.26	26.54 ± 2.38	0.052
Gestational age (weeks)	25.12 ± 1.33	25.28 ± 0.89	0.62
Pre-gestational body weight (kg)	61.38 ± 7.72	65.52 ± 5.00	0.029
Pre-gestational BMI (kg/m^2)	23.56 ± 2.66	25.86 ± 2.55	0.003
HbA1c (%)	4.79 ± 0.47	5.38 ± 0.74	0.001
Fasting glucose (mmol/L)	4.33 ± 0.39	6.18 ± 1.10	<0.001
1-h glucose (mmol/L)	7.21 ± 1.26	12.52 ± 2.80	<0.001
2-h glucose (mmol/L)	6.61 ± 1.22	12.15 ± 2.51	<0.001
Fasting insulin (μIU/mL)	12.46 ± 2.16	15.20 ± 3.49	0.002
1-h insulin (μIU/mL)	18.74 ± 1.73	20.87 ± 5.44	0.072
2-h insulin (μIU/mL)	13.40 ± 3.94	26.22 ± 5.60	<0.001
HOMA-IR	2.40 ± 0.48	4.18 ± 1.27	<0.001

Results are shown as means ± SD; N, number of cases; statistical significance $p < 0.05$.