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Association between Birth Weight and Galanin Concentrations in Maternal Plasma, Amniotic Fluid and Umbilical Cord Blood in Normal Pregnancies and Pregnancies Complicated By Gestational Diabetes

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Abstract

Background: As Galanin (GAL) is secreted by the human placenta, it might be involved in fetal growth; in addition, its action on glucose homeostasis suggests an association with Gestational Diabetes Mellitus (GDM).

Objectives: To examine whether maternal, fetal or amniotic fluid GAL concentrations i) are associated with birthweight and ii) differ between uncomplicated pregnancies and pregnancies complicated with GDM.

Study design: GAL concentrations were measured in maternal plasma and umbilical cord blood of 77 healthy pregnant women and 30 pregnant women with GDM at labour. GAL concentrations were also measured in amniotic fluid in both groups when possible. ELISA assay was used to determine the concentrations of the peptide.

Results: GAL concentrations in maternal circulation were higher than those in the umbilical cord and the amniotic fluid. In uncomplicated pregnancies, a positive correlation was present between GAL in umbilical cord and both neonatal birthweight (r=0.312, p=0.006) and placental weight (r=0.354, p=0.002). No such associations were present in pregnant women with GDM. Maternal, fetal or amniotic fluid GAL concentrations did not differ between uncomplicated and GDM-complicated pregnancies.

Conclusion: Fetal GAL concentrations may constitute an index of fetal growth, although this association was not sustained in pregnancies complicated by GDM. Maternal GAL concentrations cannot be used as an index of glucose intolerance.

Keywords: Amniotic fluid; Birthweight; Galanin; Diabetes; Gestational; Pregnancy

Introduction

Birthweight is an important predictor of an individual's morbidity and mortality, regarding not only short-term consequences, but also development of diseases in childhood and adult life [1,2]. Among the many factors affecting fetal growth and birthweight, neuropeptides play an important role [1].

Galanin (GAL) is a neuropeptide consisting of 30 amino acids in humans and 29 in other mammals [3]. It is synthesized mainly in the central nervous system (hypothalamus and anterior pituitary gland), nevertheless, GAL is expressed in a variety of organs, such as pancreas, intestine, adrenal medulla and placenta [3]. Three receptor subtypes, GalR (GAL Receptors) 1 to 3, members of the G-Protein-Coupled Receptor (GPCR) superfamily, are widely distributed in the nervous system and pancreas [4]. The main biological actions of human GAL include regulation of neurotransmission and promotion of neurogenesis, as well as metabolic, endocrine and reproductive functions [4]. Moreover, GAL has been associated with immune processes, inflammation, cancer, emotional behaviour, alcohol consumption and processes of learning and memory [5].

GAL family includes the bioactive peptides GALP (Galanin-Like Peptide), GMAP (Galanin-Message Associated Peptide) and alarin. These peptides are involved in many biological functions, such as energy homeostasis, reproduction and neurotransmission. Their effects are mediated *via* the same three receptor subtypes (GalR 1-3) [4,6]. GAL peptides are derived from a pre-pro-precursor molecule as typically occurs with regulatory peptides [6].

The investigation of the role of GAL during pregnancy began nearly 20 years ago [7]. In rats, GAL is firstly seen in trophoblast cells by the time of implantation. Its expression in the conceptus is increasing during the first 11 days, after which concentrations are declining rapidly [7]. Differentiated cells continue to secrete GAL, however, it seems that fetal GAL derives mainly from the mother's plasma GAL. GAL derived from the pituitary gland increases during the second half of pregnancy, possibly due to the high concentrations of plasma estradiol [7].

In the human placenta, GAL is mainly expressed in the cells of the decidual interface, supporting its potential role in placental function and fetal development [8]. GAL is also expressed in the developing

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embryos, GAL immune-reactive neurons were seen in the supra- and medial mammillary nucleus in human fetuses of 27-39 gestational weeks [9]. Other studies present conflicting results about pregnant women and their developing foetuses regarding the origin of GAL expression [10].

According to our recent review, there is evidence for an association between GAL and fetal growth [10]. It has been demonstrated that umbilical cord blood GAL concentrations are higher compared with those in maternal plasma and positively correlated with birth weight at term [11]. GAL concentrations in fetal circulation were not associated with neonatal fat mass, neither with placental mass. Correlation was also found between GAL concentrations in maternal circulation and maternal Body Mass Index (BMI) [11]. The association between amniotic fluid GAL during the second trimester and neonatal birthweight in 50 singleton of term deliveries was examined in a recent prospective, observational study, suggesting GAL as a possible predictive marker of neonatal birthweight [12]. Furthermore, neonatal plasma GAL concentrations were measured post-partum in normal pregnancies and those complicated with Gestational Diabetes Mellitus (GDM) and Intrauterine Growth Retardation (IUGR) [13]. GAL concentrations did not differ significantly among the three groups, a finding that is in contrast with experimental models of fetal programming [14].

There is recent evidence that GAL, through its actions on glucose homeostasis, is involved in the pathogenesis of Gestational Diabetes Mellitus (GDM) [15,16]. Higher GAL concentrations have been reported in pregnant women with GDM, establishing its positive correlation with glucose and BMI [17,18]. Such findings led to the proposal that GAL might serve as a novel biomarker for the prediction of GDM or add information to the current strategy for GDM screening [10].

According to the data mentioned above, a plausible hypothesis is that GAL is involved in fetal growth. However, data concerning the role of GAL in fetal growth are limited. Relevant studies include a small number of participants, while publications on GAL and GDM mainly focus on maternal concentrations of GAL [11,12,15-17].

The primary aim of the current study was to investigate whether maternal, fetal (umbilical cord) or amniotic fluid GAL concentrations are associated with birthweight in normal pregnancies. As a secondary aim, we attempt to investigate whether maternal, fetal or amniotic fluid GAL concentrations differ between uncomplicated pregnancies and pregnancies complicated with GDM, as well as to examine if the correlation between GAL concentrations and birthweight are different in GDM as compared with uncomplicated pregnancies.

Materials and Methods

Setting

The study was conducted from March 2015 to December 2016 in the labour ward of First Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Greece.

Patients

One hundred and seven pregnant women with median age of 30 years at 37-41 weeks of gestation as well as their neonates were included in this observational, cross-sectional study. All women were admitted to the labour ward due to spontaneous labour, induction of labour or elective caesarean section and have been recruited in a consecutive way. Seventy-seven of them had uncomplicated pregnancies (control group), whereas 30 women were diagnosed as having GDM (GDM group). Exclusion criteria were the presence of intrauterine growth retardation, congenital anomalies, smoking, risk factors and conditions which potentially could affect the fetal growth, multiple gestation and refusal of consent. GDM was diagnosed through a 75 g Oral Glucose Tolerance Test (OGTT) performed at 24-28 gestational weeks, if plasma glucose was exceeding 92 (fasting), 180 (at 1 h) or 153 mg/dL (at 2 h) (according to diagnostic criteria of International Association of Diabetes and Pregnancy Study Groups-IADPSG and American Diabetes Association-ADA 2010). Patients diagnosed with GDM were either diet controlled or on insulin therapy. None of them was on oral antidiabetic agents and cases with pre-existing diabetes were excluded. It should be clarified that the above cases were not stratified according to the severity of GDM, however, there was no suspected fetal growth disorder during antenatal period (small or large for gestational age fetus).

Sample size estimation

Sample size estimation was based on a previous study with similar outcomes [11]. Regarding the association between birthweight and GAL concentrations in umbilical cord blood, it was estimated that 63 uncomplicated pregnancies would achieve 80% power to detect a correlation of r=0.35 with a p-value of 0.05 [11]. In the meantime, it was decided to collect the same samples from GDM-complicated pregnancies for a pilot study, as such a study had not been performed in the past. The sample size of GDM pregnancies needed in order to detect a difference was not estimated as this was not part of the main study.

Ethics

The relevant registered protocol included the clinical characteristics of each case (antenatal history, intrapartum details, neonatal parameters) as well as the measurements of the samples planned to be studied. Research procedures were explained and all participants gave written consent. Study protocol was approved by the Bioethics Committee of Aristotle University of Thessaloniki, Greece (Reference Number: 217-07/09/2015). The study was carried out in accordance with "The Code of Ethics of the Declaration of Helsinki".

Study parameters

Each patient was initially classified into the appropriate group (normal or GDM). Demographic and clinical characteristics of the participants were recorded: Age, gravidity, parity, personal history, BMI before gestation, BMI at delivery and weight gain during pregnancy. After labour, the following parameters were recorded: Mode of delivery, neonatal gender, birthweight, body length, thickness of skinfold, placental weight and possible obstetrical or neonatal complications. Neonates were weighted using a digital balance after the cord was clamped. The placenta was also weighted using a digital balance after the cord was clamped at the proximal end. The skinfold thickness was measured in a small number of cases (15 out of 107) due to technical reasons.

Sample collection and handling

Maternal blood samples (10 mL) were collected from a peripheral vein (usually the median cubital) before labour in EDTA tubes containing aprotinin. Samples of amniotic fluid (10 mL) were collected in cases of unruptured membranes and clear amniotic fluid. A syringe was used in order to collect the amniotic fluid during vaginal delivery or caesarean section just before artificial rupture of membranes. Blood or meconium-stained samples were excluded in order to ensure that there was no contamination.If membranes were already ruptured on

admission, amniotic fluid was not obtained in such cases. Amniotic fluid samples were collected in plain tubes not containing aprotinin. Umbilical cord blood samples (10 mL, obtained from the placental part) were collected after labour in EDTA tubes containing aprotinin. All samples were centrifuged immediately and stored at 80°C until measurement (less than 6 months). The stored samples included the supernatant plasma from maternal and umbilical cord blood as well as the amniotic fluid samples.

Peptide assay

GAL was measured using a commercially available ELISA kit (enzyme immunoassay) "Human Galanin Elisa kit" (Blue Gene Biotech, Shanghai, China, Catalogue Number E01G0033), designed for the quantitative determination of Human GAL including samples from serum, plasma, body fluid. According to the manufacture's specification, the range of the assay was 0-1000 pg/mL and the average sensitivity 1.0 pg/mL. Intra- and inter-assay Coefficient of Variation (CVs) were <10%. All measurements were performed in duplicate and the mean of the two measurements was considered.

Statistical analysis

The normality of the data was tested with Kolmogorov-Smirnov test. The linear association between the parameters evaluated was tested with Pearson and Spearman rho correlation coefficient, in cases of parametric and non-parametric distribution of the data, respectively. Based on the normality of the results, independent samples t-tests or Mann Whitney U tests were used to determine difference between groups. The comparison of the percentages among groups was done with Fisher's exact test. A significance level of $p \leq 0.05$ was used in all comparisons. Data analysis was done using the statistical software SPSS 21.

Results

The main maternal and neonatal characteristics are presented in Table 1.

Parameter	Control	GDM	p-value
	n=77	n=30	
Maternal age (years)	29.0 ± 5.4	32.0 ± 4.6	0.019
Gestational age (weeks)	39.0 ± 1.1	38.0 ± 0.7	<0.001
Parity [n (%)]			
0	38 (49%)	12 (40%)	0.534
1	24 (31%)	11 (37%)	0.715
2	12 (16%)	3 (10%)	0.625
3	3 (4%)	2 (6.5%)	0.968
≥ 4	0 (0%)	2 (6.5%)	0.146
Sex of neonate [n (%)]			
Male	44 (57.1%)	13 (43.3%)	0.285
Female	33 (42.8%)	17 (56.6%)	0.285
Mode of delivery [n (%)]			
Vaginal delivery	43 (55.8%)	12 (40%)	0.21
Caesarean section	34 (44.1%)	18 (60%)	0.206
Gestational weight gain (kg)	15.4 ± 5.0	12.9 ± 6.8	0.075
BMI at delivery (kg/m^2)	29.7 ± 4.7	32.7 ± 6.5	0.026
Neonatal birthweight (g)	3335 ± 393	3217 ± 364	0.19
Neonatal body length (cm)	50.9 ± 2.2	50.6 ± 2.0	0.5
Placental weight (g)	557.0 ± 104.0	557.5 ± 115.0	0.984

*Data are presented as mean ± SD, unless indicated otherwise, GDM: Gestational Diabetes Mellitus

Table 1: Maternal and neonatal characteristics.

GAL concentrations

In the total study population, as well in the control (uncomplicated) group, GAL concentrations in maternal plasma were significantly higher compared to those in umbilical cord and amniotic fluid. However, in GDM group no difference was detected among GAL concentrations in maternal plasma, amniotic fluid and umbilical cord. In addition, no difference was detected when comparing the GAL concentrations in maternal plasma, umbilical cord and amniotic fluid between the control and GDM group (Table 2).

Control group

Positive correlation was found between GAL in umbilical cord and both neonatal birthweight (r=0.312, p=0.006) and placental weight (r=0.354, p=0.002). No correlation was found between maternal plasma GAL and the BMI of pregnant women at delivery (r=0.018, p=0.878) or the weight gain during pregnancy (r=0.002, p=0.985). However, neonatal birthweight was associated with maternal gestational weight gain (r=0.369, p=0.001) (Table 3).

GDM group

There was no correlation between maternal, umbilical or amniotic fluid GAL concentrations and neonatal birthweight, body length, placental weight. Moreover, no association was shown between maternal BMI at delivery and GAL levels in maternal plasma or umbilical cord blood (r=0.039, p=0.852 and r=-0.220, p=0.291 respectively). However, a positive correlation was found between neonatal birthweight and maternal gestational weight gain (r=0.444, p=0.026) (Table 4).

n	Control	GDM	p-value
	77	30	
Maternal plasma (pg/mL)	247.5 (633.0)	243.3 (1431.8)	0.804
Umbilical cord (pg/mL)	179.6 (884.0)	161.9 (1465.9)	0.187
Amniotic fluid (pg/mL)	186.3 (375.9)	126.5 (313.3)	0.321

*Data are presented as median (range), GDM: Gestational Diabetes Mellitus

Table 2: Galanin concentrations.

	Maternal galanin	Umbilical cord galanin	Amniotic fluid galanin
Neonatal birthweight	r=-0.131	r_s=0.312	r=-0.217
	p=0.256	p=0.006	p=0.190
Neonatal body length	r=-0.189	r_s=0.133	r=-0.227
	p=0.103	p=0.253	p=0.170
Placental weight	r=-0.138	r_s=0.354	r=-0.016
	p=0.233	p=0.002	p=0.926

*r: Pearson r correlation coefficient, r_s: Spearman rho correlation coefficient

Table 3: Correlation between galanin concentrations and neonatal parameters at birth in control (uncomplicated) pregnancies.

	Maternal galanin	Umbilical cord galanin	Amniotic fluid galanin
Neonatal birthweight	r_s=0.182	r=0.072	r=-0.189
	p=0.384	p=0.734	p=0.556
Neonatal body length	r_s=0.179	r=0.076	r=0.161
	p=0.403	p=0.723	p=0.637
Placental weight	r=-0.197	r=-0.182	r=-0.414
	p=0.356	p=0.394	p=0.206

r: Pearson r correlation coefficient, r_s: Spearman rho correlation coefficient, GDM: Gestational Diabetes Mellitus

Table 4: Correlation between galanin concentrations and neonatal parameters at birth in pregnancies complicated with GDM.

Total population

A positive correlation was found between umbilical cord GAL concentrations and both neonatal birthweight (r=0.213, p=0.032) and neonatal skinfold thickness (n=15, r=0.654, p=0.021). In addition, neonatal birthweight showed statistically significant correlation with maternal weight gain during pregnancy (r=0.399, p<0.05).

Discussions

Main findings

The aims of this pilot study were to examine whether maternal, fetal or amniotic fluid GAL concentrations i) are associated with birthweight; and ii) differ between uncomplicated pregnancies and pregnancies complicated with GDM. The main findings were that in uncomplicated pregnancies, GAL in umbilical cord is positively correlated with neonatal birthweight and that maternal, fetal or amniotic fluid GAL concentrations do not differ between uncomplicated pregnancies and pregnancies complicated by GDM.

GAL concentrations during pregnancy

Research about GAL in pregnancy comes mainly from animal studies or studies in humans that involve a small number of patients [7,11,12]. GAL was detected in all samples of maternal plasma, umbilical cord blood and amniotic fluid. Maternal GAL concentrations were higher than those in the umbilical cord and the amniotic fluid. However, a previous study demonstrated the opposite: Umbilical cord GAL concentrations were higher than those in maternal circulation [11]. It is a reasonable assumption that umbilical cord GAL has both fetal and placental origin. Fetal GAL derives from the hypothalamus-pituitary and the developing gastrointestinal tract [7]. On the other hand, maternal GAL derives from the gastrointestinal tract (main source), the anterior pituitary (30% of GAL in the non-pregnant state) and the placenta [11]. During pregnancy, GAL secretion from the pituitary is increased, as it is induced by oestrogens, placental GAL is decreasing towards term due to the regression of the trophoblastic tissue [7,19]. Finally, the origin of GAL concentrations in the amniotic fluid is not clear, as research data are limited [11,12]. As a result of all the above, GAL concentrations in maternal plasma, umbilical cord and amniotic fluid may present high variability, as they depend on complex pathophysiologic mechanisms and interactions among the pregnant woman, the foetus and the placenta.

GAL concentrations in pregnancies complicated with GDM

The group of pregnancies complicated by GDM, although small in size, was selected as GDM can cause foetal development disorders, such as macrosomia [20]. In addition, GAL has been involved in glucose homeostasis [15]. Data about GAL in GDM are limited, focusing almost exclusively on maternal concentrations [15-18]. In our study, maternal GAL concentrations did not differ from those in uncomplicated pregnancies. Other studies suggest that maternal GAL concentrations are higher in women with GDM compared to those with normal OGTT [16-18]. In addition, in our study, umbilical cord GAL concentrations were similar in GDM and control groups. This observation agrees with a previous study of similar design [13].

GAL and birthweight

In the group of uncomplicated pregnancies, positive correlation was found between umbilical cord GAL and birthweight, in agreement of a similar study of smaller sample size [11]. We have also demonstrated positive correlation between umbilical cord GAL and placental weight. Such a correlation is not surprising, given the expression of GAL from the placenta [8]. As the placental weight is an independent prognostic factor of perinatal outcome, the above correlation is of great clinical importance [21]. On the other hand, the correlation mentioned above was not detected in the GDM group. As a possible explanation, GDM may induce alterations in anatomy, histology and physiology of the placenta, which might change its mass and function at a molecular level [22,23].

GAL and maternal BMI

In our study, no correlation was detected between maternal GAL concentrations and BMI at birth, despite the evidence for a positive correlation, in both uncomplicated and GDM pregnancies [11,15-17]. Maternal BMI at birth depends on various genetic, environmental and metabolic factors, such as maternal weight before conception, nutrition and level of physical activity during pregnancy. Moreover, pregnancy itself induces metabolic and endocrine changes, resulting in increases in body weight and percentage of adipose tissue [24]. Meanwhile, in pregnancies complicated by GDM, the diagnosis of the latter is followed by lifestyle modifications and insulin administration, that could affect the BMI at birth.

GAL and weight gain

Maternal weight gain during pregnancy was positively correlated with neonatal birthweight in all groups, confirming previous studies [25,26]. Furthermore, positive correlation was demonstrated between umbilical cord GAL and skinfold thickness of the neonate, an index of neonatal fat mass. The expression of GAL in the paraventricular nucleus of the hypothalamus has been associated with the consumption of fat as well as with the percentage of body fat, GAL concentrations have been found to be higher in patients with obesity [27,28].

Study limitations

The present study was an observational, cross-sectional one, including small number of patients (especially regarding the group of GDM) measuring GAL concentrations at the time of delivery only. Therefore, no conclusions can be drawn regarding maternal and fetal GAL concentrations throughout the pregnancy. In addition, as only full-term, uncomplicated pregnancies were included, no conclusions can be drawn regarding cases of Intrauterine Growth Retardation (IUGR). Nevertheless, as the women were recruited in a consecutive way, according to the inclusion criteria, they could be considered as representative of the general population.

As regards the GDM subgroup specifically, the subjects were not stratified by the severity or the required treatment, a fact which could affect the results of the study. When comparing GAL concentrations in uncomplicated and GDM pregnancies, it should be considered that the two groups differed in the maternal age and BMI at delivery (Table 1). Both factors could potentially affect the outcomes.

It is obvious that the main independent (GAL concentrations) and dependent (neonatal birthweight) study parameters are affected by a wide spectrum of confounders, such as genetic, endocrine and environmental factors of the mother and the fetal-placental unit, which are difficult to be assessed in any study [1]. Finally, regarding the association of GAL with stress, the mode of delivery (vaginal delivery or caesarean section) may also affect GAL concentrations.

Conclusion

Fetal GAL concentrations may constitute an index of fetal growth,

as they are positively correlated with birthweight and placental weight. This association was not sustained in pregnancies complicated by GDM. Maternal GAL concentrations cannot be used as an index of glucose intolerance, as there was no difference between uncomplicated pregnancies and pregnancies complicated by GDM. It is obvious that additional studies of prospective design, conducted in large cohorts of women, are needed to elucidate the role of GAL in fetal growth and carbohydrate metabolism during pregnancy. Such studies could evaluate GAL in target populations, such as maternal obesity and Small (SGA) or Large for Gestational Age (LGA) neonates.

Ethics Approval

Approval by the Bioethics Committee of the Aristotle University of Thessaloniki, Thessaloniki, Greece (reference Number: 217-07/09/2015).

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