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Research Article

Regulation of Decidual PRL, Vasoinhibins and Vascularization in the Placenta during Gestation in the Diabetic Rat

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Abstract

Maternal diabetes increases the risk of adverse fetal and maternal pregnancy outcomes. The risk has been associated with an elevation in the placental content of vasoinhibins known for their antiangiogenic effect, resulting from decidual prolactin (dPRL) cleavage in shorter fragments, in diabetic women and streptozotocin (STZ)-induced diabetic rats, during pregnancy and gestation close to term. Bone-morphogenetic-protein-1 (BMP-1) is one of the peptidases promoting PRL cleavage. The aim of the study was to monitor the vascularization and the production of dPRL and vasoinhibins, earlier, at key gestational stages in the placenta of diabetic rats.

Wistar rats received at the 7th day of gestation (G7), streptozotocin (STZ, n=18) or nicotinamide (NCT) plus STZ (n=22) or vehicle (n=24) and were sacrificed at G14 and G17. BMP-1 gene expression, dPRL and vasoinhibins content, and vascularization were assessed in placentas by RT-quantitative PCR, western blotting and histological analysis respectively dPRL content was higher at G14 in the diabetic groups compared to control rats. The higher dPRL content was associated with enlarged capillary diameters and vascular modification within placenta at G14 and G17 compared to controls. At G17, compared to controls, the vascular modification was accompanied by reduced vasoinhibins content in the placenta. In line with this decrease, the expression of placental Bmp-1 was reduced.

This study suggests a role for dPRL and vasoinhibins in the placental vascularization dysfunction observed during last third of gestation in rat maternal diabetes.

ABBREVIATIONS

BMP-1: Bone-Morphogenetic-Protein-1; DPRL: Decidual Prolactin; G: Day of Gestation; NCT: Nicotinamide; PAS: Periodic Acid Schiff; PRL: Prolactin; STZ: Streptozotocin

INTRODUCTION

Type 1 diabetes is a risk factor for adverse pregnancy outcomes. The relative risks for congenital malformations, perinatal morbidity, preterm delivery and abnormal birth weight are two- to five-folds increased when compared to the general population [1]. In 1989, the St. Vincent's declaration set a five-year target for approximating outcomes of pregnancies in women with diabetes type 1 or type 2 or gestational diabetes compared to those of the background population [2]. During pregnancy, the placenta is an essential organ for fetal metabolism and the long-term health of the offspring. Maternal nutritional and metabolic disturbance during pregnancy leads to changes in placental structure and function which may contribute to abnormal supply of nutrients and oxygen into the fetal circulation and to hormonal disorders [3]. Perturbed fetal development caused by placental dysfunction increases susceptibility to develop metabolic diseases in childhood and adult life [4-6].

The placenta produces several hormones, including decidual prolactin (dPRL) in humans and rodents [7]. While the 23-kDa full-length prolactin (PRL) is an angiogenic hormone [8,9],

the shorter 14-16-kDa (in rat) or 15-17-kDa (in human) PRL fragments called vasoinhibins resulting from a PRL cleavage by peptidases including the bone-morphogenetic-protein-1 (BMP-1) have antiangiogenic properties [9-14].

We have recently reported an increase in dPRL gene expression and vasoinhibin content in the placenta of women with type 1 diabetes at the end of gestation compared to controls [15]. Streptozotocin (STZ)-induced diabetes in gestating rats mimics human maternal diabetes [16,17]. STZ does not affect fetal pancreatic metabolism whereas it rapidly induces diabetes by causing beta cell death in the dam pancreas. Moreover, marginal traces of STZ are found in the feto-placental compartment [18]. Induction of diabetes in dams causes a reduction in offspring weight [15]. The perturbed fetal development is accompanied by an increase of vasoinhibin content and placental hypovascularization at the 21st day of gestation (G21) in STZ-induced diabetic rat models.

Using transcriptomic analysis, it was demonstrated that the levels of RNA expression of the PRL family members – such as placental lactogen, but excepting decidual prolactin-related protein – and of all the known proteases able to cleave PRL – such as cathepsin D or metalloproteases, but excepting *Bmp-1* - were not different in the diabetic placenta compared to controls [15]. These results highlight a possible impact of placental vasoinhibin content on placental vascularization and fetal development.

In this regard, the goal of this animal study conducted in diabetic dams was to investigate the expression of dPRL and its vasoinhibins and of placental BMP-1 at key gestational stages prior to term and the possible involvement in placental vascularization.

MATERIALS AND METHODS

Ethics statement

The study was conducted in accordance to the French regulations for animal experiments and following the ethical rules issued by the European Directive 2010/63/EU of the European parliament and by the council on protection of animals used for scientific purposes translated in French law on the 1st of February 2013 (2013/118). All animal procedures were approved by the Lille 2 University and Hospital Department of Experimental Facility Research (DHURE, DDPP/59-35010) and performed in the same department. All efforts were made to ensure adequate animal care and to minimize animal suffering. All animal procedures were made by experienced and qualified personnel.

Animal study

Three-month-old female Wistar rats were obtained from Janvier (Le Genest Saint Isle, France). The rats were housed individually and fed ad libitum with a standard chow diet (SAFE 04, 2,900 cal/g, containing 16% protein, 3% fat, 60% carbohydrates (UAR, Augy, France)) under controlled temperature (22 ± 1°C) and 12/12 h light/dark cycles.

On the 7th day of gestation (G7), three groups of animals were established: the control group (n=24, i.p. injection of NaCl 0.9% and citrate buffer 0.1 M pH 4.5, sequentially), the streptozotocin group (STZ; Sigma-Aldrich, St Quentin-Fallavier, France) (n=18, i.p. injection of STZ, 65 mg/kg body weight in citrate buffer 0.1M pH 4.5), and the nicotinamide group (NCT, Sigma-Aldrich, St Quentin-Fallavier, France)-STZ (n=22, i.p. injection of nicotinamide, 75 mg/kg body weight in NaCl 0.9%). Daily fed capillary blood glucose (ACCU-CHEK Performa Glucometer, Roche Diagnostics, Mannheim, Germany) and weight were assessed from G7 in dams from the three groups.

Collection of blood, tissue samples and metabolic measurements

Dams were sacrificed equally at G14 and G17, by fast decapitation with guillotine without using any previous drug to preserve fetal vitality in accordance with European and French regulations (2010/63/EU). Eight to 12 pups were present for each dam with their own placenta. Dams with more than 12 or less than 8 pups were excluded from the study. Collection of clinical data and blood and tissue sampling were performed at each sacrifice for all of the dams in each group. Maternal blood, from fed animals, was collected for glucose (ACCU-CHEK Performa glucometer, Roche) assessment. Fetuses were removed with their respective placenta and weighed. Placentas were weighed, washed in phosphate buffered saline (PBS) then transferred in RNA later (Qiagen, Courtaboeuf, France) for gene expression analysis, snap frozen in liquid nitrogen and stored at -80°C for protein analysis, or fixed in paraformaldehyde (PFA) 4% for histological analysis.

Placenta gene-expression analyses

For measurement of gene expression, five placentas were randomly selected from each dam. Total RNA was isolated using RNeasy® kit (Qiagen, France). RNA quantification and quality were assessed by UV spectrophotometric analysis with Nano Drop (Thermo Fischer Scientific, Illkirch, France) and, the Agilent Bioanalyzer capillary electrophoresis system (Agilent technologies France, Massy, France). The gene expression assessment was performed by TaqMan quantitative RT-PCR as previously described [15]. Total RNA was reverse-transcribed using a high-capacity cDNA RT kit (Applied Biosystems, Foster city, CA). Assays were carried out using Universal Master Mix (Applied Biosystems) and TaqMan probes (Table 1). PCR was achieved on an Applied Biosystems 7900HT detection system (cycling program included 10 min incubation at 95°C followed by 40 cycles at 95°C). Data (Cycle threshold [Ct] values) were extracted from each assay with the SDS software tool (Applied Biosystems). Each assay was run in triplicate for each placental RNA sample. Gene expression was normalized with beta 2 microglobulin (B2M) gene.

Placenta western blotting analysis

Total protein was prepared as previously described [15]. For western blotting, 70µg of proteins from the three animal groups were loaded into 12% SDS-PAGE. Three to five placentas were randomly selected from each dam. Western blotting analysis was performed using rabbit anti-PRL (1/200, Santa Cruz Biotechnology) and mouse anti-alpha-tubulin (1/5000, Sigma) antibodies. PRL extracted from rat pituitary gland was used as positive control as decidual PRL and pituitary

PRL have similar and molecular weight structure [19]. After being transferred on a nitrocellulose membrane (Hybond-ECL, Amersham BioSiences, Chalfont, UK), the proteins were detected using horseradish-conjugated secondary antibody (1/5000; Santa Cruz Biotechnology) and Chemiluminescence Supersignal (Pierce). Densitometric analysis was performed using Image J software (National institutes of Health, Maryland, USA) and data were normalized for alpha-tubulin. Vasoinhibins were quantified by using the sum of 14- and 16-kDa PRL fragments as previous described [15].

Placenta histological analyses

Three to five placentas from each dam were randomly selected. Five µm-thick sections were deparaffinized with xylene. For each placenta, sections were stained with hematoxylin and eosin (HE) and with periodic acid Schiff (PAS). The capillary diameter (µm) was estimated using an ocular micrometer (Leica microsystem). Five microscopic fields (objective 40x) were analyzed. Fetal capillaries were defined as those containing nucleated erythrocytes (maternal vascular spaces contain only mature erythrocytes which lack a nucleus) [20].

Statistical analyses

Analysis of the normality of the data was performed using the Shapiro–Wilk test. Analysis using one-way ANOVA was performed for parametric data followed by Bonferroni correction for the comparisons between groups. Kruskal–Wallis test followed by Dunn's multiple comparison test for the comparison between groups was performed for non-parametric data and very small sample sizes. Data are presented as their median ± interquartile range (IQR) for non-parametric data or as their mean ± SEM for parametric data. All statistical analyses were performed using Graph Pad Prism 5.0 (Graph Pad Software, Inc, San Diego, USA). P-value ≤ 0.05 was considered statistically significant.

RESULTS

Maternal diabetes and intrauterine growth restriction (IUGR) by G14

To achieve the objective of the study, we used the diabetic rat model previously described induced by STZ or NCT-STZ [15]. STZ causes maternal diabetes without directly affecting the fetal pancreas as the GLUT2 glucose transporter, through which STZ triggers beta cell destruction, is not expressed during early pancreas development [16,21].

STZ-induced diabetes is usually severe [22]. Injection of low doses of STZ is further inefficient to lead to less severe hyperglycemia [17,23]. Since severe hyperglycemia induced by STZ can lead to serious complications and adverse effects, we have used a model of rat with mild hyperglycemia. This was achieved by STZ followed by NCT. Co-administration of NCT with STZ lowers severe hyperglycemia, insulinopenia, and fetal abnormalities and mortalities [15,24-26]. As expected, rats displayed hyperglycemia after STZ injection in both diabetic groups (Table 2). A significant body weight loss occurred at G17 in the STZ group compared to controls (Table 2). The NCT-STZ treatment led to less severe hyperglycemia when compared to STZ [15,24,25]. In this regard, hyperglycemia from the NCT-STZ-

Table 1: TaqMan probes used for RT-PCR in the rat placenta.

ID name	Accession number	Assay ID	Gene Name
Rat *Bmp1*	Rn01466024_m1	NM_ 031323.1	Bone Morphogenetic
			Protein 1
Rat *B2M*	Rn00560865_m1	NM_012512.2	Beta-2 microglobulin

Table 2: Analysis of dams' clinico-biological parameters.

	Dams' weight (g)				Dams' blood glucose (mmol/l)			
	Median ± (IQR)			p	Median ± (IQR)			P
	C	STZ	NCT-STZ		C	STZ	NCT-STZ	
G7	250.5 ± (261-233)	256 ± (290-246)	253 ± (266.5-235)	C vs STZ NS C vs NCT-STZ NS STZ vs NCT-STZ NS	6.49 ± (7.15-6.05)	6.98 ± (7.5-6.07)	6.38 ± (7.23-5.91)	C vs STZ NS C vs NCT-STZ NS STZ vs NCT-STZ NS
G14	292 ± (307-272)	260 ± (283.3-227.3)	260 ± (275-238)	C vs STZ NS C vs NCT-STZ NS STZ vs NCT-STZ NS	4.95 ± (5.11-4.62)	33 ± (33-32)	28.16 ± (33-24.48)	C vs STZ p<0.001 C vs NCT-STZ p<0.001 STZ vs NCT-STZ NS
G17	335 ± 369.5-302)	258 ± (276.5-244.8)	294 ± (338-282.5)	C vs STZ p<0.01 C vs NCT-STZ NS STZ vs NCT-STZ P<0.05	4.75 ± (4.95-4.62)	33 ± (33-33)	27.20 ± (28.99-26.24)	C vs STZ p<0.001 C vs NCT-STZ P<0.001

treated rats was lower compared to the STZ-treated rats (p< 0.001) at G17, and the body weight loss of NCT-STZ dams was not present at G17 when compared to the STZ group (Table 2).

In the control group, fetal weight increased from G14 to G17 (Figure 2A). A similar gain was seen in the diabetic groups from G14 to G17 (Figure 1A). However, in the diabetic group's fetal weight was lower throughout (G14 and G17) compared to controls (Figure 2A). Parallel to fetal development, placental weight increased in the control group from G14 to G17 (Figure 1B). As observed for fetuses, placental weight was lower in the STZ and NCT-STZ groups at G14 (p<0.001) compared to controls. At G17, placental weight remained lower in the NCT-STZ group compared to the control group whereas no difference was noted between the STZ group and the controls (Figure 1B).

In line with this, we observed greater glycogen deposit in the junctional zone and the labyrinth trophoblastic layer of placentas from STZ and NCT-STZ at G17 without any between-group differences at G14 when compared to controls (Figure 1C).

In line with this, we observed greater glycogen deposit in the junctional zone and the labyrinth trophoblastic layer of placentas from STZ and NCT-STZ at G17 without any between-group differences at G14 when compared to controls (Figure 1C).

Vasoinhibins were decreased at G17 in placentas of diabetic rats

The expression of placental Bmp-1 was similar in both the control and diabetic groups at G14 (Figure 2A). Placental Bmp-1 gene expression was however reduced at G17 in the STZ (p<0.01) and NCT-STZ (p<0.001) groups when compared to the control group (Figure 2A). Western blotting analyses confirmed the presence of vasoinhibins in the placentas from the diabetic and control groups (Figure 2B). The expression of vasoinhibins was similar at G14 between all groups whereas it was lower at G17 in the placentas of STZ (p<0.001) and NCT-STZ (p<0.01) groups compared to controls (Figures 2B and 2C).

Changes in dPRL products abundance were associated with placental vascular dysfunction in diabetic pregnant rats

Placental vascularization was assessed by hematoxylin-eosin sections and stereological analysis of capillary diameter and vascular surface area. In line with the unmodified placental vasoinhibins level, placental vascularization was similar at G14 in the diabetic groups compared to controls (Figure 3A). Nevertheless, at G14, greater capillary diameter was observed in diabetic placentas compared to controls (Figure 3B) associated with higher angiogenic dPRL expression at the protein level (Figure 2D). In the diabetic groups, placentas became hypervascularized at G17, in line with the drop of placental vasoinhibins level, with increased mean capillary diameter compared to controls (Figures 3A and 3B). dPRL expression at the protein level at G17 was similar in all groups (Figure 3D).

DISCUSSION

Gestational diabetes increases the risk of maternal, fetal and neonatal complications. The risk may be linked to placenta dysfunction that release inappropriate levels of hormones or products levels. We have previously shown that the expression of dPRL and vasoinhibins is dysregulated in placentas of women with diabetes. Similar changes were observed in two gestating rat models of diabetes induced by STZ and NCT-STZ [15]. While hyperglycemia caused by STZ is severe and rapidly leads to complications, diabetes induced by the combination of STZ and NCT is less severe. Because the rat models of diabetes mimicked the human placenta dysfunction and hyperglycemia and insulin secretion variation of diabetic type 1 women, in this study we chose these models for monitoring the changes

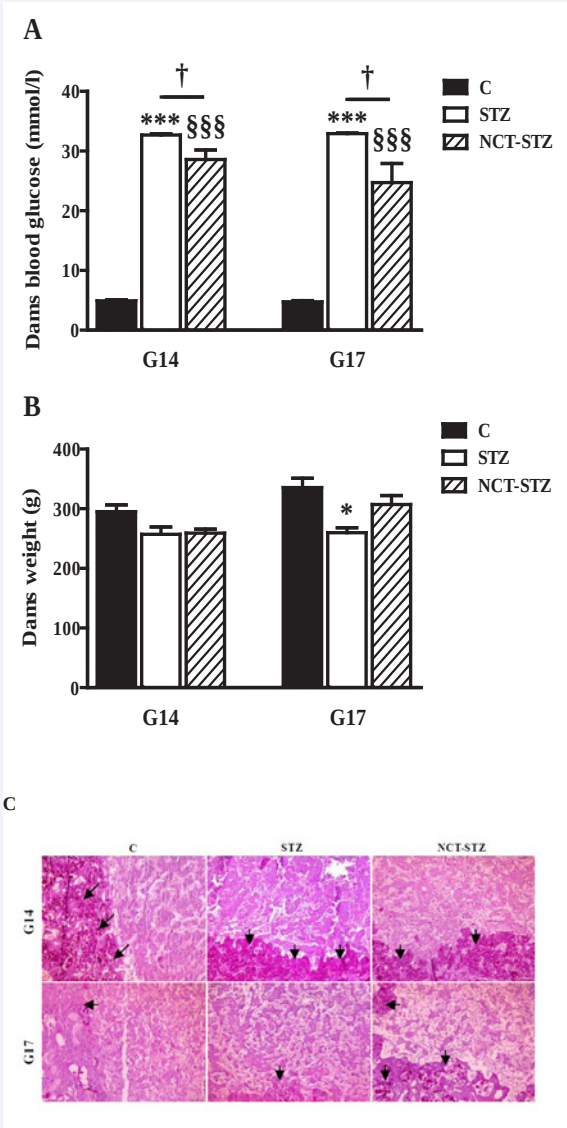

Figure 1 Analysis of fetal and placental weights at G14 and G17. Fetal weight (A) and placental weight (B) at G14 and G17. Data are expressed as means ± SEMs and are significantly different at *p<0.001, ***p<0.001 STZ vs C; §§§p<0.001 NCT–STZ vs C. C : n=120 (G14) ; n=128 (G17) ; STZ ; n=95 (G14) ; n=98 (G17) ; NCT-STZ ; n=110 (G14) ; n=115 (G17)

Placental staining sections with Periodic Acid Schiff (PAS) at G14 and G17 (C). Magnification× 100. Presence of placental glycogen deposits after PAS staining (red-purple coloration)

STZ: Streptozotocin; NCT: Nicotinamide; C: controls. C: n=24 (G14); n=24 (G17); STZ ; n=18 (G14) ; n=18 (G17); NCT-STZ ; n=33 (G14); n=33 (G17)

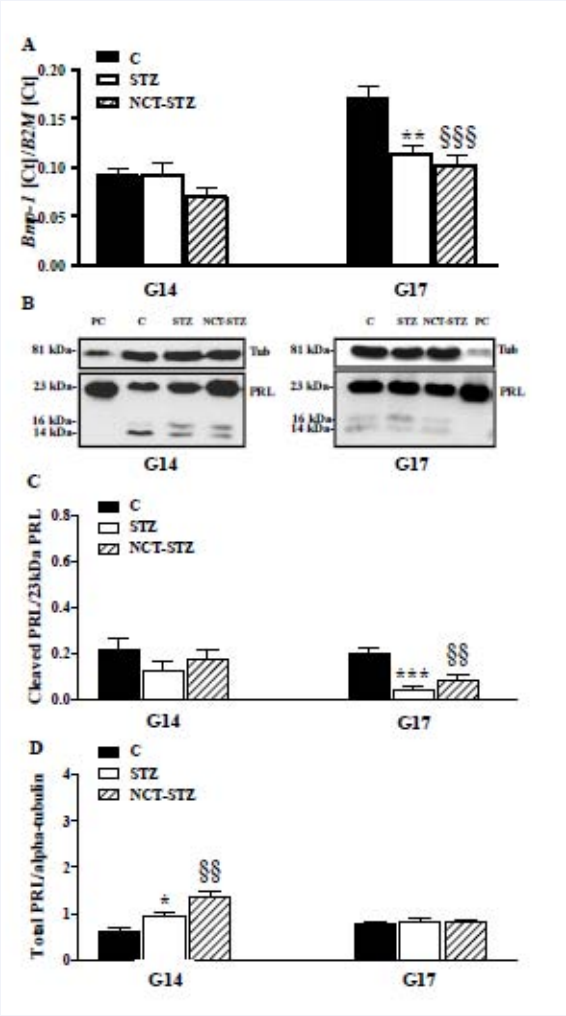

Figure 2 Analysis of decidual PRL cleavage at G14 and G17. Placental Bone Morphogenetic Protein-1 (Bmp-1) gene expression normalized to beta 2 microglobulin (B2M) (A). C: n=60 (G14); n=60 (G17); STZ; n=45 (G14) ; n=45 (G17); NCT-STZ ; n=55 (G14); n=55 (G17). Representative western-blot of decidual prolactin (PRL) proteolytic
BCC STZ NCT-STZ PC81 kDa-23 kDa-16 kDa-14 kDa-TubPRLPC C STZ NCT-STZTubPRL81 kDa-23 kDa-16 kDa-14 kDa-DG14G17A0.00.20.40.60.8CSTZNCT-STZE14E17E21§§****§Cleaved PRL/23kDa PRL01234CSTZNCT-STZ*§§E14E17E21Total PRL/alpha-tubulinG14G17G17G140.000.050.100.150.20CSTZNCT-STZG14G17**§§§Bmp-1[Ct]/B2M[Ct]
products (B). PC: positive control. Extracted prolactin (PRL) from rat pituitary gland was used as PC.The relative molecular mass of each band is shown on the left. Quantification of cleaved PRL products to 23-kDa PRL ratio (C). Quantification of total PRL normalized to alpha-tubulin amount (D). Cleaved PRL represents the sum of ≈16-kDa PRL and ≈14-kDa PRL fragments. Data are means ± SEM and are significantly different at *p<0.05 STZ vs C; ***p<0.001 STZ vs C; §§p<0.01NCT–STZ vs C.STZ: streptozotocin; NCT: nicotinamide; C: controls. C: n=36 (G14); n=36 (G17); STZ; n=30 (G14); n=31 (G17); NCT-STZ; n=33 (G14); n=34 (G17)

in dPRL and vasoinhibins at G14 and G17. Herein, we show that the modification in placental vascularization was found to be associated with changes in dPRL and vasoinhibins expression at G14 and G17. These modifications are not caused by the severity of diabetes as the results were found both in diabetic rats with severe (STZ group) and mild (NCT-STZ group) hyperglycemia.

Placental vascularization in rat starts between 12 and 14 days of gestation, reaching maximum size at approximately G17, thus allowing optimal maternal vascular spaces and overgrowth of fetal capillaries [20,27]. This is associated with a decrease in trophoblast layers and the intervascular barrier [20]. Increased vascularization facilitates maternal blood flow until term.

In gestational diabetes, the diffusion distance between the maternal and fetal systemic circulations is increased due to the thickening of the trophoblastic layer [28]. Fetoplacental vascular growth is then compromised in pregnancies, possibly leading to intrauterine growth restriction (IUGR). Nonetheless, it has been demonstrated that in maternal diabetes around G14, the placenta is able to compensate for its own growth restriction by up regulating its nutrient supply [29]. The mechanism of compensation may include an increase in capillary diameter since we observed an increase in the diameter of placental capillaries in diabetic rats at G14. dPRL is an angiogenic hormone that stimulates trophoblast invasiveness and cell migration at early pregnancy *in vitro* [30]. In this study, we showed that the increase of capillary diameters is associated with the rise of dPRL content in pregnant diabetic rats at G14. Future studies will be needed to determine whether the elevated dPRL accounts for the placental vascularization in pregnancy of diabetic rats.

Our findings revealed that the increase of capillary diameter persisted and was associated with placental hypervascularization at G17. In addition, the phenotypical change in the placenta

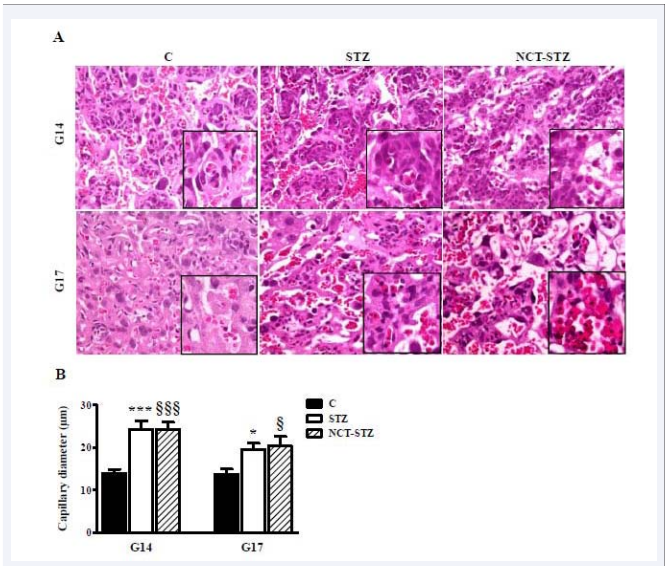

Figure 3 Placental histological analyses at G14 and G17.
Placental histological sections stained by Hematoxylin-Eosin in controls, in STZ and NCT-STZ groups (A) at G14 and G17. Stereological analysis of capillary diameter at G14 and G17 (B). The capillary diameter (µm) was estimated using an ocular micrometer (Leica microsystem). Five microscopic fields (objective 40x) were analyzed. Fetal capillaries were defined as those containing nucleated erythrocytes (maternal vascular spaces contain only mature erythrocytes which lack a nucleus)
Data are means ± SEM and are significantly different at *p<0.05 STZ vs C; ***p<0.001 STZ vs C; §p<0.05NCT–STZ vs C; §§§p<0.001 NCT–STZ vs C.Magnification×200 and in the square ×400. STZ: streptozotocin; NCT: nicotinamide; C: controls. C: n=60 (G14); n=58 (G17); STZ; n=45 (G14) ; n=43 (G17); NCT-STZ ; n=54 (G14); n=55 (G17)

was accompanied by a decrease in vasoinhibins, a hormone known for its antiangiogenic effect. Reduction of vasoinhibins in the placenta may be the consequence of the drop of placental *Bmp-1* gene expression level. Unlike, as previously shown, the placental vascularization was much reduced and the placental vasoinhibins content was inversely increased at the delivery [15]. Thus a reduction in the amount of placental vasoinhibins might contribute to the compensatory placental vascularization anti-diabetes mechanism.

CONCLUSION

In conclusion, our study describes some early changes in placental dPRL and vasoinhibins production associated with changes in placental vascularization during gestational diabetes. Identifying the mechanisms underpinning placental dysfunction, and thereby affecting fetal growth in gestation diabetes, would contribute to future development of innovative treatments to prevent intra-uterine growth restriction and adverse outcomes for offspring.

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REFERENCES

1. Kennelly MA, McAuliffe FM. Prediction and prevention of Gestational Diabetes: an update of recent literature. Eur J Obstet Gynecol Reprod Biol. 2016; 202: 92-98.
2. Diabetes care and research in Europe: the Saint Vincent declaration Diabet Med. 1989; 7: 360.
3. Jansson T, Ylven K, Wennergren M, Powell TL. Glucose transport and system A activity in syncytiotrophoblast microvillous and basal plasma membranes in intrauterine growth restriction. Placenta. 2002; 23: 392-399.
4. Aceti A, Santhakumaran S, Logan KM, Philipps LH, Prior E, Gale C, et al. The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. Diabetologia. 2012; 55: 3114-3127.
5. Bunt JC, Tataranni PA, Salbe AD. Intrauterine exposure to diabetes is a determinant of hemoglobin A(1)c and systolic blood pressure in pima Indian children. J Clin Endocrinol Metab. 2005; 90: 3225-3229.
6. Fetita LS, Sobngwi E, Serradas P, Calvo F, Gautier JF. Consequences of fetal exposure to maternal diabetes in offspring. J Clin Endocrinol Metab. 2006; 91: 3718-3724.
7. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000; 80: 1523-1631.
8. Clapp C, Lopez-Gomez FJ, Nava G, Corbacho A, Torner L, Macotela Y, et al. Expression of prolactin mRNA and of prolactin-like proteins in endothelial cells: evidence for autocrine effects. J Endocrinol. 1998; 158(1): 137-144.
9. Struman I, Bentzien F, Lee H, Mainfroid V, D'Angelo G, Goffin V, et al. Opposing actions of intact and N-terminal fragments of the human prolactin/growth hormone family members on angiogenesis: an efficient mechanism for the regulation of angiogenesis. Proc Natl Acad Sci U S A 1999; 96: 1246-1251.
10. Clapp C, Martial JA, Guzman RC, Rentier-Delure F, Weiner RI. The 16-kilodalton N-terminal fragment of human prolactin is a potent inhibitor of angiogenesis. Endocrinology. 1993; 133: 1292-1299.
11. Clapp C, Gonzalez C, Macotela Y, Aranda J, Rivera JC, Garcia C, et al. Vasoinhibins: a family of N-terminal prolactin fragments that inhibit angiogenesis and vascular function. Front Horm Res. 2006; 35: 64-73.
12. Ge G, Fernandez CA, Moses MA, Greenspan DS. Bone morphogenetic protein 1 processes prolactin to a 17-kDa antiangiogenic factor. Proc Natl Acad Sci U S A. 2007; 104: 10010-10015.
13. Gonzalez C, Parra A, Ramirez-Peredo J, Garcia C, Rivera JC, Macotela Y, et al. Elevated vasoinhibins may contribute to endothelial cell dysfunction and low birth weight in preeclampsia. Lab Invest. 2007; 87: 1009-1017.
14. Triebel J, Bertsch T, Bollheimer C, Rios-Barrera D, Pearce CF, Hufner M, et al. Principles of the prolactin/vasoinhibin axis. Am J Physiol Regul Integr Comp Physiol. 2015; 309: R1193-R1203.
15. Perimenis P, Bouckenooghe T, Delplanque J, Moitrot E, Eury E, Lobbens S, et al. Placental antiangiogenic prolactin fragments are increased in human and rat maternal diabetes. Biochim Biophys Acta. 2014; 1842: 1783-1793.
16. Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia. 2008; 51: 216-226.
17. McEvoy RC, Andersson J, Sandler S, Hellerstrom C. Multiple low-dose streptozotocin-induced diabetes in the mouse. Evidence for stimulation of a cytotoxic cellular immune response against an insulin-producing beta cell line. J Clin Invest. 1984; 74: 715-722.
18. Reynolds WA, Chez RA, Bhuyan BK, Neil GL. Placental transfer of streptozotocin in the rhesus monkey. Diabetes. 1974; 23: 777-782.
19. Prigent-Tessier A, Tessier C, Hirosawa-Takamori M, Boyer C, Ferguson-Gottschall S, Gibori G. Rat decidual prolactin. Identification, molecular cloning, and characterization. J Biol Chem. 1999; 274: 37982-37989.
20. Coan PM, Ferguson-Smith AC, Burton GJ. Developmental dynamics of the definitive mouse placenta assessed by stereology. Biol Reprod. 2004; 70: 1806-1813.
21. Schnedl WJ, Ferber S, Johnson JH, Newgard CB. STZ transport and cytotoxicity. Specific enhancement in GLUT2-expressing cells. Diabetes. 1994; 43: 1326-1333.
22. Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi S, Farhangi A, Verdi AA, et al. Induction of diabetes by Streptozotocin in rats. Indian J Clin Biochem. 2007; 22: 60-64.
23. Portha B, Levacher C, Picon L, Rosselin G. Diabetogenic effect of streptozotocin in the rat during the perinatal period. Diabetes. 1974; 23: 889-895.
24. Cisse O, Fajardy I, ckes-Coopman A, Moitrot E, Montel V, Deloof S, et al. Mild gestational hyperglycemia in rat induces fetal overgrowth and modulates placental growth factors and nutrient transporters expression. PLoS One. 2013; 8: e64251.
25. Masiello P, Bergamini E. Nicotinamide and streptozotocin diabetes in the rat. Factors influencing the effectiveness of the protection. Experientia. 1977; 33(9): 1246-1247.
26. Masiello P, Broca C, Gross R, Roye M, Manteghetti M, Hillaire-Buys D, et al. Experimental NIDDM: development of a new model in adult rats administered streptozotocin and nicotinamide. Diabetes. 1998; 47: 224-229.
27. Watson ED, Cross JC. Development of structures and transport functions in the mouse placenta. Physiology (Bethesda). 2005; 20: 180-193.
28. Vambergue A, Fajardy I. Consequences of gestational and pregestational diabetes on placental function and birth weight. World

J Diabetes. 2011; 2: 196-203.

29. Angiolini E, Fowden A, Coan P, Sandovici I, Smith P, Dean W, et al. Regulation of placental efficiency for nutrient transport by imprinted genes. Placenta. 2006; 27 Suppl A: S98-S102.

30. Stefanoska I, Jovanovic KM, Vasilijic S, Cujic D, Vicovac L. Prolactin stimulates cell migration and invasion by human trophoblast *in vitro*. Placenta. 2013; 34: 775-783.

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