Bradykinin B1 receptor overexpression is positively correlated with increased histidine decarboxylase (HDC) activity – a potential role in the pathophysiology of diabetic placenta.

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Abstract: Hyperhistaminaemia and increased bradykinin have been found in diabetic placentae. Both, histamine and bradykinin are well known mediators of inflammation. Bradykinin may stimulate mast cell degranulation, increasing the local histamine level. Bradykinin B1 receptor shows involvement in the inflammatory response, whereas the B2 receptor mediates most of the effects induced by kinins. In this study we examined comparatively (diabetes class C vs normal pregnancy) correlations between placental HDC activity, histamine concentration, and placental bradykinin receptors B1 and B2 expression. Sixteen diabetic placentae and 16 normal (control) placentae were collected (Group I and II, respectively). Activity of HDC was assayed in placental samples obtained in a standardized manner, using a modified method of Endo. Histamine concentrations in placental cuts were estimated fluorimetrically, whereas expression of B1 and B2 was examined in immunostained paraffin sections, using quantitative morphometry in the areas matched in mean vascular density. Mean HDC activity in diabetic placenta was significantly ($p<0.05$) increased compared to controls (3.97 ±0.25 vs 2.88 ±0.15 nmol/h/g ±SEM). Histamine concentration was also significantly increased in diabetes (387 ±25.3 vs 239 ±14.3 ng/g of wet weight ±SEM; Group I and Group II, respectively). Mean expression of the B1 was augmented in diabetes and reached 289.8% of the value observed for Group II ($p<0.05$). Mean expression of B2 receptors was similar in both studied groups. Increased HDC activity may be responsible for some of the pathophysiologic events observed in diabetic materno-placento-fetal compartment. HDC-dependent histamine elevation may change locally vascular properties by influence on bradykinin receptors expression. Proinflammatory changes mediated via B1 should be expected rather, than modified vasomotor reactivity related to B2. Angiogenic properties of histamine and kinins may also be of great importance hin diabetic placental tissue.

Keywords: histidine decarboxylase, histamine, bradykinin receptors, human placenta, diabetes class C, pregnancy

1 Introduction

Diabetes mellitus is one of the most common medical complications of pregnancy [1]. Diabetes evokes a complex series of events that results in structural and functional abnormalities in many tissues and body compartments, including uterofetoplacental unit [2]. For that reason, diabetes in pregnancy can have serious consequences for the mother and the growing fetus. The placenta is the first of the fetal organs to develop and possess several unique and critical functions, precisely modulated during the course of pregnancy [3]. Therefore, normal placentation and development of the placental vascular network are crucial for adequate blood supply to the fetus and preservation of fetal well-being [4,5]. Human placenta establishes the interface for nutrient and gas exchange between the maternal and fetal circulation, initiates maternal recognition of the allograft tissues, and influences maternal cardiovascular and metabolic functions through the production of paracrine and endocrine factors [6,7,8,9]. The role of many placental biologically active compounds, both released from previously formed tissular reservoirs as well as produced locally within the blood is still under investigation. Some of these studies are targeted on pathophysiology of diabetic complications [10,11].

It was proved, that diabetic placenta undergoes a variety of structural and functional changes. Their nature and extent depend on a range of variables including the quality of glycemic control in the period directly before conception and during the course of gestation, the type of diabetes as well as its duration. The White classification, named after Priscilla White who pioneered in research on the effect of diabetes

types on perinatal outcome, is widely used to assess maternal and fetal risk [12, 13](see Tab. 1). It distinguishes between gestational diabetes (type A) and diabetes that existed prior to pregnancy (pregestational diabetes). These two groups are further subdivided according to their associated risks and management [14]. Maternal ketoacidosis and iatrogenic hypoglicaemia may be life threatening, both to the pregnant woman and the fetus. Fetuses or infants of mothers with diabetes are at greater risk for several problems, especially if blood glucose levels are not carefully controlled, including the following: birth defects, stillbirth (fetal death), macrosomia, birth injury (due to the baby's macrosomia), hypoglycemia after delivery and respiratory distress [15]. The placenta of the diabetic patient has attracted much interest largely because it is thought that placental damage may be partially responsible for the unduly high incidence of fetal complications that occur in pregnancies complicated by diabetes mellitus [16]. There are still some controversies and discussions about the importance of such a damage, while another group of researchers proposed the term "placental remodeling" as more adequate for description of placental morphology, reflecting the action of compensatory mechanisms [17,18,19]. Class C diabetes in pregnancy (after White) is the last stage without recognized vascular changes in light microscopy [20].

Human placental tissue contains a moderate amount of histamine. First description of this compound was given in 1910 by Dale and Laidlaw [21]. Histamine (2-[4-imidazolyl]-ethylamine) is a biogenic amine, derived from the decarboxylation of histidine in reaction catalyzed by the pyridoxal phosphate containing L-histidine decarboxylase (HDC; EC 4.1.1.22). In peripheral tissues, histamine is stored in mast cells, eosinophils, basophils, enterochromaffin cells and probably also in some specific neurons [22]. Vesicular structures (granules) of mast cells are the main source of placental histamine, which may be released during the process known as mastocyte degranulation.[23,24]. Among many other mast cell-derived substances, placental histamine acting via specific histamine receptors is considered as important pro-inflammatory mediator, local regulator of the vascular resistance and permeability as well as the growth (angiogenic) factor [18,25,26]. All discovered so far histamine receptor subtypes (named H1, H2, H3, and H4) have been localized in the human placenta, [25,27,28].

The results of our previous comparative studies showed, that in diabetes class C (after White) an increased density of the villous network of placental microvessels correlates with higher histamine concentration and increased number of mast cells [29,30].

GESTATIONAL DIABETES (the beginning during pregnancy):		
Class		*Description*
A1		**Gestational diabetes; diet controlled**
A2		**Gestational diabetes; insulin controlled**
DIABETES EXISTED BEFORE PREGNANCY (pre-existed diabetes)		
Class		*Description*
B		**Onset at age 20 or older or with duration of less than 10 years**
C	**C1**	**onset at age 10–19; no vascular lesions**
	C2	**or duration of 10–19 years; no vascular lesions**
D		**Onset before age 10 or duration greater than 20 years**
E		**Overt diabetes mellitus with calcified pelvic vessels**
F		**Diabetic nephropathy**
R		**Proliferative retinopathy**
RF		**Retinopathy and Nephropathy**
H		**Ischemic heart disease**
T		**Prior kidney transplant**

Table 1.

Classification of White for diabetes during pregnancy in humans [20]. It is important to mention, that class C is the last stage without recognized vascular changes in light microscopy.

The nonapeptide bradykinin is the final product of the kinin system and is split from a serum alpha-2-globulin precursor by the kallikreins (EC 3.4.4.21) and also by trypsin (EC 3.4.4.4) or plasmin (EC 3.4.4.14) [31]. Bradykinin is a potent endothelium-dependent vasodilator for most vessels, except for the placental, causes contraction of non-vascular smooth muscle, increases vascular permeability and also is involved in the mechanism of pain. In some aspects, it has similar actions to that of histamine. Moreover, some amount of bradykinin is present in the granules of mast cells [32].

The bradykinin receptor family is a group of G protein coupled receptors (GPCRs) whose principal ligand is the protein bradykinin. There are two bradykinin receptors: B1 and B2 [33,34]. However, a third receptor designated B3 has been proposed based on variation in affinity or inactivity of antagonists [35]. B1 protein may be synthesized de novo following tissue injury and receptor binding leads to an increase in the cytosolic calcium ion concentration, ultimately resulting in chronic and acute inflammatory responses [36].

The B2 receptor is ubiquitously and constitutively expressed in healthy tissues and mediates most of the effects induced by kinins [37]. Its activities include stimulation of phospholipase C to increase intracellular free calcium and an inhibition of adenylate cyclase. Furthermore, the receptor stimulates the mitogen-activated protein kinase pathways. Angiotensin potentiates bradykinin action on B2. The role of B2 receptors in cross-talk between placental renin-angiotensin system (RAS) and the local kinin-kallikrein system is still under investigation [37,38]. Interestingly, kallidin also signals through the B2 receptor [39].

Increased levels of bradykinin have been reported in diabetes [40, 41]. Moreover, it was proved that bradykinin induces mast cell degranulation, leading to increase in the local histamine concentration [42].

2 Aim of the study

The aim of the present investigation was to examine comparatively correlations between placental HDC activity, histamine concentration and placental bradykinin receptors B1 and B2 expression in diabetes class C versus normal pregnancy.

3 Materials and methods

This study was conducted in compliance with international and local laws of human experimentation and the project was approved by the local ethics committee. All subjects provided written ethical consent to the collection and use of their tissues, according to the standards published by British Medical Research Council as "Human tissue and use of biological samples: operational and ethical guidance 2001 (includes Addendum to MRC 2001 guidance following the Human Tissue Act 2004)".

3.1 Placental tissue collection

Sixteen placentae were obtained after pregnancies complicated by diabetes class C (after White) and gestationally matched with 16 placentae collected after normal-course pregnancies (group I and group II, respectively) [10]. The control of glycemia in all cases was satisfactory: the levels of fraction of glycosylated hemoglobin (HbA_{1C}) in all trimesters of diabetic pregnancy were kept within the normal range (5–7.5%). The gravidas in both groups were nulliparas and the mean gestational age amounted to 252 ± 6 days. All newborns in group I were delivered by elective cesarean sections in fetal interest, while in group II the operative indications were: high myopia or pelvic longitudinal lie of the fetus (breech presentation). Five specimens of placental tissue were excised in a standardized manner: two from the region contiguous to fetal surface of the placenta (the first – from place of umbilical cord insertion, the next – from peripheral region), and three from the region contiguous to maternal surface (the first one – from the central part, the next two – from peripheral regions of the placental maternal surface) (see Fig. 1). The samples obtained after cesarean section were at once frozen in carbon dioxide snow for histamine concentration measurement. Simultaneously, further samples were fixed in formalin, embedded in paraffin wax and cut at 5 μm, before staining with hematoxylin/eosin and immunostainings.

3.2 Assessment of HDC activity

Tissular activity of HDC was assayed in placental samples obtained in a standardized manner. A modified method, descripted previously by Endo was applied [43]. Briefly, histamine-free enzyme solution containing HDC has been obtained after homogenization with phosphorylated cellulose and centrifugation. Then, newly formed histamine after incubation of the enzyme solution with histidine (1mM) was separated by chromatography and quantified fluorometrically as an indicator of HDC activity.

3.3 Measurement of histamine

Histamine concentrations in placental cuts were estimated using fluorimetric method [44]. Briefly,

determination of histamine was based on a precolumn derivatization with o-phthaldialdehyde, using reversed phase high performance liquid chromatography in perchloric acid extracts. A fluorescence detection system was used: excitation was set at 360 nm and emission was read at 455 nm of wavelenghts. The detection limit was 250 pg per sample.

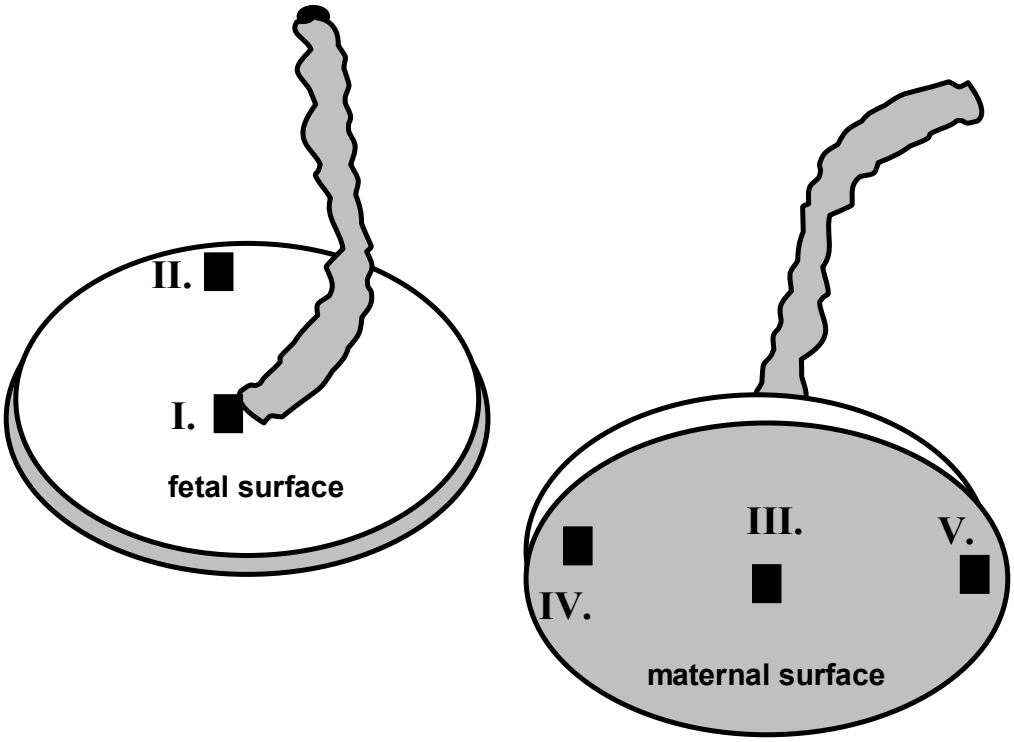

Figure 1.

Location of samples collected in standardized manner from the maternal surface of the placenta (I-III) and from the fetal surface (IV-V). The mean weight of samples 10.31 ±0.93g.

3.4 Immunohistochemistry of B1 and B2

In order to visualize bradykinin B1 and B2 receptors in the paraffin sections (N = 72 for each group, for each type of the receptor staining), a standard immunohistochemical staining procedures were applied. Rabbit bradykinin B1 receptor antibody (B1R; extracellular domain; reacting with Hu, Ms, Rt; dilution of 1:500) and rabbit bradykinin B2 receptor antibody (B2; recting with Hu, Ms, Rt; dilution of 1:500) were used as the primary antibodies, respectively. Goat anti-rabbit IgG antibodies were used as biotinylated secondary antibody (0.5% v/v). Both, the primary and secondary antibodies were manufactured by Acris Antibodies GmbH, Germany. The visualization of primary anti-receptor antibodies was done using the StreptABComplex/HRP Duet (Dako Cytomation, Glostrup, Danmark) following the procedure recommended by the producer, where 3,3'-diaminobenzidine served as a chromogen. The negative controls for immunostainings were prepared by replacement of the primary antibodies by normal rabbit preimmune IgG diluted with phosphate buffered saline, containing 3% bovine serum albumin at the same protein concentration as that used for the primary antibodies.

3.5 Mean density of placental microvessels

Assuming, that the accurracy of bradykinin receptors expression measurement may be significantly affected by local differences in density of vascular system, in both groups we examined comparatively vascular density–matched samples (tolerated range of discrepancy was ± 5%) [45]. Mean density of placental microvessels was measured in calibrated areas of the placental paraffinized sections stained with hematoxylin/eosin. Light microscopy with computerized morphometry for quantitative analysis (Quantimet 500+C image analysis system provided by Leica, Cambridge Ltd., Cambridge, UK) was used. The mean Vascular / Extravascular Tissular (V/EVTI) was the main parameter of the vascular density [46,47]. The picture analysis procedure consisted in measurement of the total vascular area. The total

lumen area of all types of identified vessels was summed up. In order to eliminate technical error caused by unaxial section of vessel the lowest value of Ferret's diameter was accepted as the diameter of a single lumen. V/EVTI represents the ratio, which reflects intensity of vascularization. Each preparation underwent three area analyses; the single area measured with the picture analyzer amounted to 721320 μm^2. The total number of preparations amounted to 288 for each group.

3.6 Expression of B1 and B2

After immunostaining, B1 and B2 receptors expression was estimated using quantitative computerized morphometry (Image analysis system with Quantimet 500+C software by Leica, UK) under the light microscopy [47]. All morphometric procedures were carried out twice by two independent observers, and the average results recorded. Intensity of immunostaining was evaluated using mean colour saturation parameter and thresholdings in grey-level histograms. Expression of bradykinin B1 and B2 corresponded to the total immunostained calibrated area of examined sections, where colour saturation comprises segmentation-separation criteria for objects. Single analysed image area was 721320 μm^2. In each group 216 visual fields were analysed for each type of bradykinin receptor (3 visual fields per single paraffin slide). In order to assure optimal accuracy of measurements, following factors have been controlled or monitored: illumination, power supply, warming up, shading correction, averaging of image intake, hue, luminance, relation of illumination to quantiffication of area percentage of positively staining structures.

3.7 Statistical analysis

Mann-Whitney's U-test was applied. The results were expressed as means ±SEM or mean percentage values ±SEM. Differences between group I (diabetes) and II (normal-course pregnancy) were deemed statistically significant if $p < 0.05$.

4. Results

Mean HDC activity in group I was significantly ($p<0.05$) increased compared to controls (3.97 ±0.25 vs 2.88 ±0.15 nmol/h/g ±SEM) as shown in Figure 2.

The expressions of bradykinin receptors B1 and B2 are presented in Figure 3. Mean expression of the B1 was augmented in diabetes and reached 289.8% of the value for group II ($p<0.05$). The differences in mean expression of B2 receptors were non significant.

Histamine concentration in diabetes class C (group I) was significantly increased compared to normal controls from group II (387 ±25.3 versus 239 ±14.3 ng/g of wet weight ±SEM); (see Fig. 4).

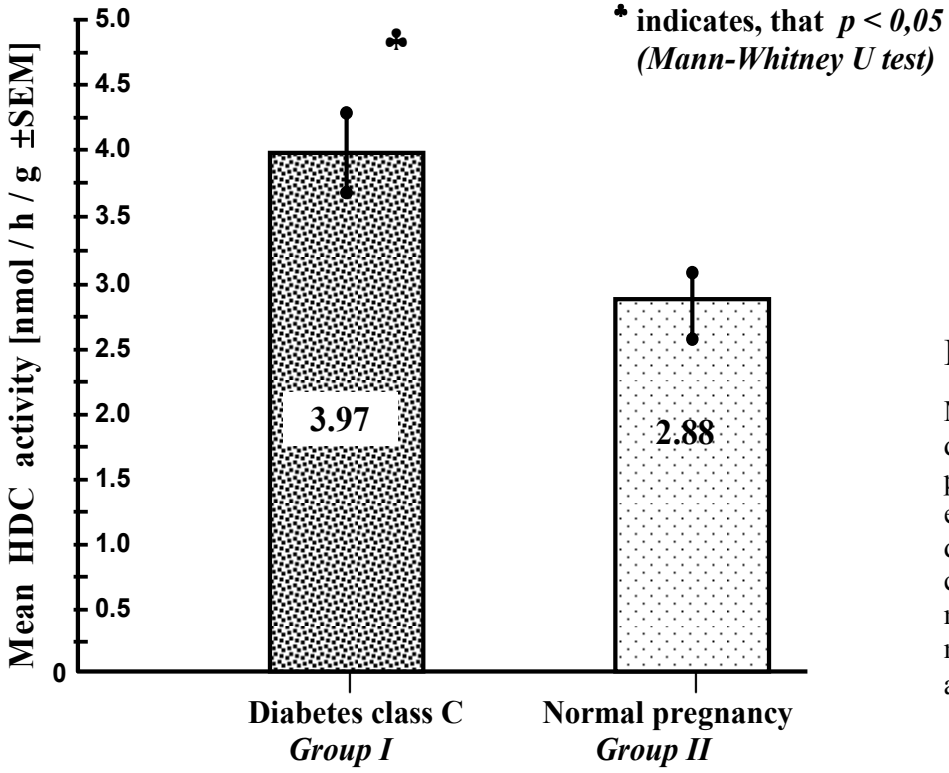

Figure 2.

Mean activity of histidine decarboxylase (HDC) in placental tissue after elective cesarean section: diabetes versus non-complicated gestationally matched pregnancies. The mean gestational age amounted to 252 ± 6 days.

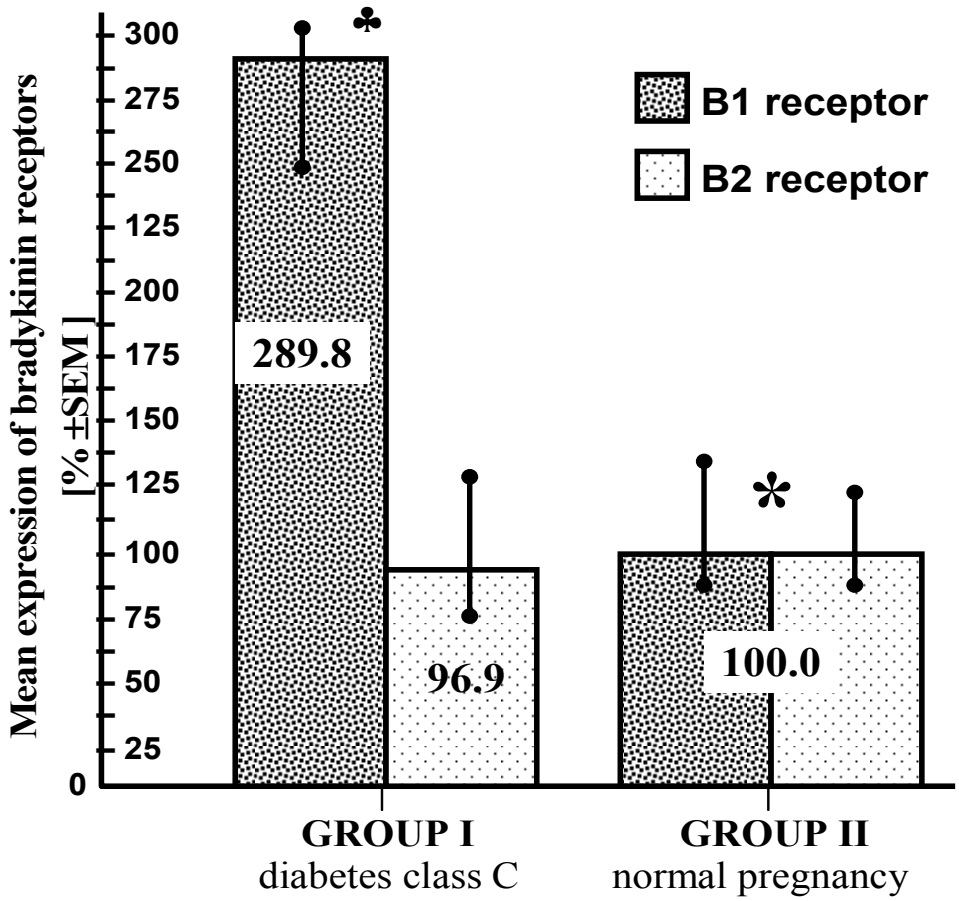

Figure 3.

Diabetes White class C (Group I) vs normal course of pregnancy (Group II): the mean expression of bradykinin receptors B1 and B2. *Mean values obtained for normal pregnancy (0.022 ±0.0017 for B1, and 0.019 ±0.0013 for B2; abstract numbers ±SEM) were taken as 100%.

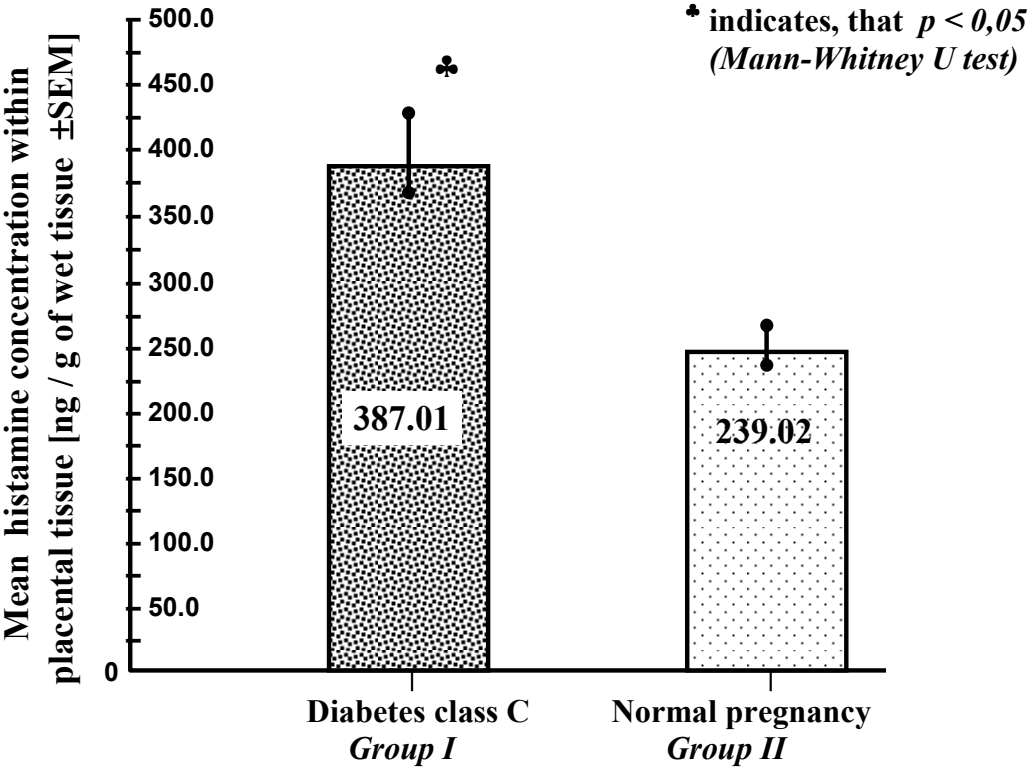

Figure 4.

Diabetes class C (according to White classification; Group I) vs normal course of pregnancy (Group II): the mean histamine concentration within placental tissue.

5. Discussion

The placenta is a complex and still poorly understood organ, which plays the central metabolic role in pregnancy. In addition to synthesizing various hormones it regulates the transport of maternal fuels to the fetus and facilitates maternal metabolic adaptations to different stages of pregnancy [48]. Considering its central position within uterofetoplacental unit, the placenta is exposed to metabolic endocrine and/or perfusion derangements. It is very likely, that diabetic environment influences receptors, transporters, ion channels and other molecules on both placental surfaces, being in contact with both maternal syncytiotrophoblast) and fetal (endothelium) circulation [49]. Diabetes mellitus during pregnancy is associated with dysregulation of the oxygen and glucose metabolic pathways, both of which affect placental villous growth and function [50,51]. Moreover, changed properties of the human trophoblast and diabetic placental tissue, including abnormal angiogenic response, increased susceptibility to hypoxia and hypoxia-related apoptotic triggers, may significantly affect fetal well-being [52,53,54]. It was reported, that hyperglycemia may be a key factor evoking apoptosis in the placental trophoblast, and therefore, is relevant to diabetic placenta function [55,56] It has been reported that in many diseases, including pregnancy complicated by diabetes, autoimmunity is at least partially accompanied by shifted (typically: down-regulated) apoptotic activity within affected tissue [57].

The crucial question is still open: whether the placenta adapts to the diabetic environment with the ultimate result of protecting the fetus from the adverse diabetic environment or whether placental changes are responsible for pathophysiology of the fetus and adverse fetal outcome, despite improvement in the care of diabetic women.

Clinical observations and histopathological studies of the placenta have confirmed an increased incidence of inflammatory reactions in diabetes [18]. Based on neutral protease composition, placental mast cell heterogeneity in diabetec class C may also be important. Previously, we reported the shift of the quantitative balance in mast cell tryptase positive-chymase negative/ tryptase positive-chymase positive subtypes towards increase of the last mentioned, and increased total number of placental mast cells [58]. According to Welle's observation, tryptase seems to participate in pro-inflammatory mast cell function, whereas chymase seems to be more involved in inflammatory reactions [59]. Moreover, knowing that bradykinin levels in diabetes may be elevated and that bradykinin degranulates mast cells, a chronic pro-inflammatory conditions should be suspected within diabetic placenta [40,42]. Degranulation of mast cells will produce additional local increase in bradykinin level. Thus, hyperhistaminaemia in diabetic placentae, supported by HDC hyperactivity, may change vascular properties, influencing bradykinin B1 receptor. This mechanism of vicious circle may be responsible for some complications reported in diabetic pregnancy. For example, it should be evaluated if increased rate of major birth defects in infants of diabetic mothers is related to mitogenic properties of bradykinin acting via B1 receptor [60].

It is important to mention about the role of histamine degradation in the placental tissue. Histamine can be metabolized by two alternative ways: oxidative deamination by enzyme diamine oxidase (DAO; EC 1.4.3.6; former name – histaminase) or ring methylation by histamine-N-methyltransferase (HNMT; EC 2.1.1.8) [27,61]. Whether histamine is catabolized by DAO or HNMT, is supposed to depend on the localization of histamine [27,62]. It has been proposed, that DAO might be responsible for scavenging extracellular histamine after mediator release, whereas HNMT acting as a cytosolic protein can convert histamine only in the intracellular space of cells [27,63,64]. DAO has been identified as the main enzyme for histamine catabolism at the feto-maternal interface [25]. DAO at the feto-maternal unit is supposed to serve as a metabolic barrier to prevent excessive entry of bioactive histamine into the maternal and fetal circulation as well as to impede prolonged exposure of decidual cells [25]. Persistently low or decreasing concentrations of DAO in the plasma have been shown in many complicated pregnancies, including gestosis/preeclampsia and diabetes, compared with normal pregnancies [65,66]. Thus, imbalanced hyperhistaminaemia related to increased amount of HDC in diabetic placental tissue may lead to increased risk of spontaneous and threatened abortion, preeclampsia and premature rupture of the fetal membranes [18,29,67].

Augmented expression of bradykinin B1 receptors without significant changes in B2 expression observed in our study may also suggest pro-inflammatory changes. According to the results of independent authors, B1 receptors are not present in any significant amount in normal tissues and their expression is often inducible rather than constitutive. Kinin B1 receptor-mediated responses are upregulated in a time- and protein production-dependent process [68]. Some experimental data suggest that diabetes is a pathological condition that could induce B1 expression. We can speculate that induction of B1 is secondary to increased mast cell number in placental tissue. However, the patomechanism for mast cell

number increase is still under investigation Insulin-dependent diabetes often derives from an autoimmune response, implicating an overproduction of cytokines such as IL-1β and TNF-α. Moreover, hyperglycemia and oxidative stress can also activate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). The addition of cytokines overproduction and hyperglycemia could then induce B1 expression through NF-κB [69,70].

It is important to mention, that during evaluation of the bradykinin receptors expression in both groups, placental tissue slides were matched with the vascular density. It is very likely, that increased mean vascular density in diabetic placenta will affect the results, potentiating the differences between examined groups. Angiogenic properties of histamine and bradykinin as well as of the another mast cell derived mediators influence on local vascular density in diabetes [71,72]. The growth-promoting activities of bradykinin are potentiated by insulin via calcium channel. Thus, hyperinsulinemic conditions due to insulin resistance may potentiate these actions of bradykinin [73]. Increased kininogen levels observed in plasma of diabetic patients can be corrected by administration of insulin [74]. Knowing from the results of others, that insulin may activate kallikrein-kinin system, the role of insulinotherapy should be taken into account. It seems resonable to choose diet controlled patients in diabetic class A1 and compare with patients who received insulin (e.g. White class A2). This issue awaits further placental study. Another line of investigation suggests that kinins exert protective effects in diabetes models in rodents as inhibitors of kininases improved the sensitivity to insulin [39,40].

It should be noticed, that we studied histamine concentration and bradykinin receptors expression in well-controlled White's class C placentae, that means: without significant vascular changes. Regulation of the blood flow in the human placenta by changes of the vascular resistance is made unique by the lack of sympathetic innervation in placental vessels [75]. For that reason, humoral factors (e.g. histamine, bradykinin) are more important than elsewhere. Both, histamine and bradykinin are vasoconstrictors acting within the placental vasculature. Increased local vascular resistance due to histamine excess in diabetic placenta seems to be of greater importance, because is accompanied by lowered activity of histamine degradating enzyme, monoamine oxidase (EC 1.4.3.4.) [35] and increased activity of HDC. Unchanged placental B2 receptors expression and increased activity of the placental proteases (EC 3.4.) in diabetes may attenuate vasoconstrictor activity of bradykinin, even if bradykinin is present in higher concentrations [18].

In conclusion, increased amounts of histamine in placental tissue in diabetes producing pro-inflammatory conditions may change vascular properties to the some degree by influence on bradykinin receptors expression and vice versa (i.e. bradykinin may affect action of histamine). Pro-inflammatory reactions mediated via B1 should be expected rather, than changed vasomotor reactivity related to B2. Angiogenic properties of histamine and kinins should also be considered.

Influence of another signaling pathways in placental environment, that lead to B1 receptor induction, especially related to the mitogen-activated protein kinase (MAPK), NF-κB and peroxisome proliferator-activated receptors (PPARs) may also be siginificant [77]. Further studies on diabetic placenta are needed to determine which mechanism predominates.

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