Placenta 35, Supplement A, Trophoblast Research, Vol. 28 (2014) S32–S38

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Review: Maternal and placental antioxidant response to preeclampsia – Impact on vasoactive eicosanoids

J.-F. Bilodeau [a,b,*]

[a] Reproductive, Maternal and Child Health, CHU de Quebec Research Center (CHUL), Québec, Canada
[b] Department of Obstetrics, Gynecology and Reproduction, Faculty of Medicine, Laval University, Quebec, Canada

ARTICLE INFO

Article history:
Accepted 22 November 2013

Keywords:
Vitamins
Glutathione
Glutathione peroxidase
Catalase
Superoxide dismutase
Coenzyme Q_{10}
Eicosanoids
Isoprostanes
Prostacyclin
Thromboxane

ABSTRACT

The abnormally developed placenta is believed to be the pathophysiological cause of preeclampsia (PE). The resulting malperfusion of the placenta in PE can be associated with fluctuations in oxygen levels, leading to oxidative stress. How then do the placenta and the circulatory system of the mother adapt and respond to the increased oxidative challenge associated with PE? Many antioxidant systems have been shown to be upregulated or downregulated in the placenta and/or the maternal circulation during PE. Such altered antioxidant response can lead to increased lipid peroxidation. Oxidation of arachidonoyl residues in phospholipids generates bioactive lipids such as F_2-isoprostanes, which are known vasoconstrictors. The consequences of changes in antioxidant status can also affect signal transduction and enzymatic pathways related to eicosanoid synthesis.

1. Introduction

In a typical uncomplicated pregnancy, the increased oxygen consumption and energy requirements for placental and fetal growth are associated with mild oxidative stress as measured in maternal plasma and urine [1]. Moreover, in pregnancies complicated by preeclampsia (PE), the oxidative stress observed is higher than in normotensive pregnancies [2]. PE is defined as the appearance of hypertension and proteinuria after 20 weeks of gestation, with an incidence of 3–7% of all pregnancies in industrialized countries. The placenta is believed to be the source for the etiology of PE, according to the classical two-stage model first described by Redman and Roberts [3]. Although there are probably numerous etiological causes for PE at the molecular level, all of these lead to oxidative stress later in gestation.

This review will first discuss the placental antioxidant response to PE-associated oxidative stress since the feto–maternal interface is at the origin of this pathology. It will next deal with the maternal response involved in the second stage of PE. Lastly, it will focus on the consequences of these antioxidant changes on the various vasoactive eicosanoid pathways, using arachidonic acid (AA) as the initial substrate. Two pathways will be specifically reviewed: the cyclooxygenase (COX) and the F_2-isoprostane pathways.

The COX pathway leads to the formation of biosynthesized prostaglandins (PG), namely $F_{2\alpha}$ and thromboxane A_2 (TXA_2), which are known vasoconstrictors, and prostacyclin (PGI_2) and PGE_2, known vasodilators [4]. The second pathway involves the non-enzymatic oxidation of AA into numerous F_2-isoprostanes [5], the most studied representative being the classical 8-iso-$PGF_{2\alpha}$ (or $iPF_{2\alpha}$-III), an accurate marker of oxidative stress [6]. When liberated from phospholipids at the *sn*-2 position by phospholipases A_2, 8-iso-$PGF_{2\alpha}$ also acts as a vasoconstrictor.

2. Evidence of placental oxidative stress in preeclampsia

PE is associated with abnormal trophoblast differentiation and invasion, resulting in an altered vascular remodeling of spiral arteries [7]. This in turn leads to reduced placental perfusion and ischemia, a source of oxidative stress [3]. Many believe that increased placental oxidative stress in PE starts as early as at the initiation of intervillous blood flow after ~8–10 weeks of gestation. At this stage, placental pO_2 rises steeply between the 10th and 12th week of gestation, with endogenous antioxidant activities like glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase rising accordingly in healthy pregnant women [8]. Despite

* CHU de Quebec Research Center (CHUL), Reproductive, Maternal and Child Health, 2705, Boulevard Laurier, Room T1-49, Quebec (PQ), Canada G1V 4G2. Tel.: +1 418 525 4444x46153; fax: +1 418 654 2765.
E-mail address: jean-francois.bilodeau@crchul.ulaval.ca.

0143-4004/$ – see front matter © 2013 Published by IFPA and Elsevier Ltd.
http://dx.doi.org/10.1016/j.placenta.2013.11.013

this, all studies have assessed placental oxidative stress only at delivery, due to obvious experimental obstacles. Not surprisingly, severe cases of PE presenting high levels of oxidative stress are often delivered much earlier than normotensive controls. Since pregnancy interruptions during the last trimester are rare, can a preterm pregnancy or a normal term pregnancy be used as a control for such severe cases of PE? The question remains partially unanswered, but careful statistical analysis and additional sampling at different gestational ages can indicate if a given marker is stable throughout the third trimester [9].

In addition to enhanced superoxide anion production by placental tissue [10] and isolated trophoblast cells *in vitro* [11], third-trimester placental homogenates from PE show 39% higher hydrogen peroxide production than normotensive controls [12]. Increased levels (1.5–3-fold) of malondialdehyde (MDA), an index of lipid peroxidation, were also observed in PE placental biopsies [13]. Elevated levels of both free and total 8-iso-$PGF_{2\alpha}$ were measured in placentas from women with PE [14]. However, Staff et al. have found a significant increase in free, but not total, 8-iso-$PGF_{2\alpha}$ in decidua basalis and placenta in PE as compared to controls [15].

Although sources of the observed oxidative stress are numerous, they might derive in part from mitochondria, which consume most of cellular oxygen. The leakage of ROS such as superoxide anion and hydrogen peroxide from the respiratory chain occurs especially upon hypoxia/reoxygenation [16]. Placental mitochondria isolated from preeclampsia have been shown to be more abundant and more susceptible to oxidation than normotensive controls, using the MDA index [17]. Other sources of oxidative stress include xanthine oxidase, which generates superoxide anion. Staining of the latter enzyme is also higher in certain trophoblasts from PE placentas than in controls [18].

3. Placental antioxidant response to preeclampsia

Placental antioxidant imbalances have been strongly associated with the pathogenesis of PE. The main placental antioxidants and enzyme activities affected in this condition are shown in Table 1. Most studies show a decrease in non-enzymatic antioxidants such as vitamin E, vitamin C, glutathione (GSH) and thioredoxin (Trx) levels in PE [13,19–21]. In addition, the antioxidant enzymatic activities of GPx, glutathione-*S*-transferase (GST), Trx reductase and SOD were shown to be decreased in PE placentas relatively to controls [11,13,19–21].

Table 1
Placental antioxidants and enzyme activities affected in PE compared to normotensive controls.[a]

	→ Unchanged [Ref.]	↑ Increased [Ref.]	↓ Decreased [Ref.]
Antioxidants			
Vitamin C (ascorbate)			[19]
Vitamin E (α-tocopherol)			[20]
Coenzyme Q_{10}		(Reviewed in Ref. [45])	
Total GSH		[65]	[13,19]
Trx		[66]	[21]
Antioxidant enzyme activities			
Catalase		[20]	
GPx	[65]		[19–21]
GST	[65]		[19]
SOD			[13,19–21] [11][b]
Trx reductase			[21]

GPx = glutathione peroxidase; GSH = glutathione; SOD = superoxide dismutase; Trx = thioredoxin.
[a] Whole placenta homogenates.
[b] Trophoblast cells for this specific reference.

More recently, the deficiencies or compensatory increases in endogenous antioxidant enzymes were pinpointed to specific isoforms of the various enzyme families (Table 2). Some studies have also controlled for the effect of labor, an important source of bias in protein and gene expression [9,22]. It has also been reported that GST of class pi was specifically decreased in the placenta and decidua of PE women [23]. It was shown that peroxiredoxin-2 and -3 were lower in the proteome of PE than in controls [24], whereas mitochondrial peroxiredoxin-3 mRNA and protein can be rather increased in PE pregnancies [25]. In addition, peroxiredoxin-6 protein level was decreased in isolated cytotrophoblasts in PE compared to controls [26].

We demonstrated that the reported decrease of SOD activity in PE placentas may be attributed to SOD1 in the absence of labor [27], and this result was also confirmed by a proteomic approach [24]. We also showed that combination of labor and PE upregulated SOD1 in fetal membranes, as well as SOD2 and SOD3 in whole placentas [27]. Moreover, we observed that GPX4 mRNA expression was deficient in PE placentas in the presence or absence of labor [22]. Likewise, Mistry et al. showed a reduction in GPx-1, GPx-3 and GPx-4 protein content in PE placental villi, using immunohistochemistry [28].

Following the above overview of the placental antioxidant response, which placental antioxidant deficiencies are the most pathophysiologically important in the etiology of PE? My preferred hypothesis is that SOD-1 and GPX-1/-3/-4 deficiencies are the key antioxidants in the progression of PE pathogenesis. Indeed, a decrease in SOD-1 level will cause an increase in superoxide anion, which then reacts with nitric oxide (NO) to form peroxynitrite. This will in turn reduce the bioavailability of NO, a vasodilator. Moreover chronic treatment with Tempol, a SOD mimetic, in the BPH/5 PE mouse model during gestation improved fetal growth and lowered maternal blood pressure at the end of gestation, compared to C57 control mice [29]. Interestingly, this model of spontaneous PE displayed impaired placentation and SOD-1 deficiency before the onset of higher blood pressure and proteinuria, which suggests an important role of SOD-1 in the early stages of PE pathogenesis [29].

GPx deficiency is likely the second key player in the etiology of PE, since decreases in this activity can be associated with the synthesis of vasoconstrictive eicosanoids such as F_2-isoprostanes and thromboxanes, which are known to be upregulated in PE placentas [30]. Moreover, since GPx are selenoproteins, their synthesis/activity is bound to selenium bioavailability. Indeed, Se deficiency in rat can be used as a model for PE [31]. Of note, Se deficiency in rat had no impact on liver and placental SOD activity. However, levels of Trx reductases, which also are antioxidant selenoproteins, are decreased, and should not be ruled out as potential players in PE pathophysiology. Trx reductases are linked to antioxidant enzyme peroxiredoxins since Trx acts as a reducing cofactor. However, peroxiredoxin-3 knockout mice show placental oxidative stress without PE-like symptoms [32]. Thus, for the time being, peroxiredoxins might therefore be excluded as major players in PE pathogenesis.

4. Evidence of maternal oxidative stress

Throughout an uneventful pregnancy, the level of 8-iso-$PGF_{2\alpha}$ increases significantly between the 26th and the 30th week from the 6- to 8-week baseline in urine, whereas this stage is reached later in plasma, namely at 37–41 weeks of gestation, i.e. just before delivery [1]. Only a few studies have looked prospectively at the potential link between PE and oxidative stress markers. One report