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Pathophysiology of Hypertension in Preeclampsia: A Lesson in Integrative Physiology

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Abstract

Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia has yet to be fully elucidated. However, it is evident that this is a complex disorder involving multiple organ systems and, by using integrative approaches, enormous progress has been made towards understanding the pathophysiology of preeclampsia. Growing evidence supports the concept that the placenta plays a central role in the pathogenesis of preeclampsia and that reduced uteroplacental perfusion, which develops as a result of abnormal cytotrophoblast invasion of spiral arterioles, triggers the cascade of events leading to the maternal disorder. Placental ischemia leads to release of soluble placental factors, many of which are classified as anti-angiogenic or pro-inflammatory. Once these ischemic placental factors reach the maternal circulation, they cause widespread activation and dysfunction of the maternal vascular endothelium that results in enhanced formation of endothelin-1 and superoxide, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide. This review highlights these links between placental ischemia, maternal endothelial activation, and renal dysfunction in the pathogenesis of hypertension in preeclampsia.

Keywords

blood pressure; pregnancy; hypertension; preeclampsia

Introduction

Preeclampsia is a pregnancy specific syndrome characterized by new onset hypertension and proteinuria (Fukui et al., 2012, Gifford et al., 2000, LaMarca et al., 2008b, Nelissen et al., 2011, Pijnenborg et al., 2008, Roberts and Gammill, 2005). Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia have not been fully elucidated. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the pathogenic process. An initiating event in preeclampsia has been postulated to be reduced placental perfusion

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that leads to widespread dysfunction of the maternal vascular endothelium and hypertension by mechanisms that remain to be defined (Fukui et al., 2012, Gifford et al., 2000, LaMarca et al., 2008b, Nelissen et al., 2011, Pijnenborg et al., 2008, Roberts and Gammill, 2005).

The hypertension associated with preeclampsia involves a complex array of factors and multiple organ systems. However, by using integrative approaches, enormous progress has been made towards understanding the pathophysiology of hypertension during preeclampsia. As mentioned before, placental ischemia/hypoxia is thought to lead to widespread activation of the maternal vascular endothelium, resulting in enhanced formation of endothelin and superoxide, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide. These endothelial abnormalities, in turn, cause generalized vasoconstriction throughout the body including the kidneys, which play a critical role in the long-term regulation of arterial pressure. Although numerous factors including genetic, behavioral, and environmental factors have been implicated in the pathogenesis of preeclampsia (Fukui et al., 2012, Gifford et al., 2000, LaMarca et al., 2008b, Nelissen et al., 2011, Pijnenborg et al., 2008, Roberts and Gammill, 2005), the main focus of this review will be on linking placental ischemia/hypoxia with endothelial cell activation and hypertension.

Abnormal Placentation and Vasculogenesis in Preeclampsia

During normal pregnancy, fetally derived cytotrophoblasts invade the maternal uterine spiral arteries, replacing their endothelium, and differentiating into an endothelial-like phenotype (Brosens et al., 1972, Damsky and Fisher, 1998, Zhou et al., 1997). This complex and not well defined process results in a conversion of the high-resistance, small-diameter vessels into high-capacitance, low-resistance vessels to accommodate adequate delivery of maternal blood to the developing uteroplacental unit. In the patient destined to develop preeclampsia, poorly understood errors in this carefully orchestrated scheme lead to inadequate delivery of blood to the developing uteroplacental unit and increase the degree of hypoxemia, normally characteristic of this organ system.

The exact mechanisms responsible for the abnormal placental trophoblast invasion and vascular remodeling in preeclampsia are unclear, but a series of studies have now appeared that enhance our understanding of these important adaptations as well as potential mechanisms that may lead to maladaptations. A number of factors have been recently implicated in placentation including the Notch signaling pathway, the transcription factor storkhead box 1 (STOX1), various components of the renin-angiotensin-aldosterone system (Todkar et al., 2012, Walther et al., 2008) and the intracellular serpin proteinase inhibitor-9 (Buzza et al., 2006).

Notch signaling may be a crucial component of the process whereby fetal trophoblast cells invade and remodel maternal blood vessels (Hunkapiller et al., 2011). The Notch signaling pathway is thought to play an important role in vasculogenesis by modulating differentiation and function during cell-cell contact. The main pathway consists of four transmembrane receptors (NOTCH1-4) and five ligands (DLL1/3/4 and JAG1/2). Binding of receptors and ligands on adjacent cells triggers serial proteolytic cleavages of the receptor, releasing the Notch intracellular domain that subsequently translocates to the nucleus to bind to transcription factors and induce downstream targets. Support of a role of Notch signaling in vascular remodeling was provided in a recent report demonstrating that the absence of *Notch2* in mice is associated with reduced spiral artery diameter (See Figure 1) and placental perfusion (Hunkapiller et al., 2011). Additional findings that peri- and endovascular cytotrophoblast often fail to express the Notch ligand, JAG1, in preeclampsia

provide further evidence that defects in Notch signaling may be important in the pathogenesis of this pregnancy complication (Hunkapiller et al., 2011).

Another recently described molecular pathway implicated in placental vascular development is the STOX1, a member of the winged helix transcription factor family. STOX1 was originally implicated in an epidemiological study that suggested increased rates of STOX1 mutation in women who experienced preeclampsia (van Dijk et al., 2005). These initial studies, while promising have been challenged by other research groups who have found little if any association of the observed polymorphisms with preeclampsia (Berends et al., 2007, Iglesias-Platas et al., 2007, Rigourd et al., 2008). While the disparity between these observations has not been fully explained, several lines of experimental *in vivo* and *ex vivo* evidence now indicate that aberrant STOX1 expression or expression of known mutant versions of the gene may have direct effects on preeclampsia associated genes. In the first instance, STOX1 overexpression in choriocarcinoma cells caused a shift in the cells' transcriptional profile mimicking the transcriptional profile observed in preeclamptic placentas (Rigourd et al., 2008). Further, the Y153H mutant identified by van Dijk et al. in their epidemiological study, has been shown to induce α -T-catenin, a cell-cell adhesion molecule known to be overexpressed in the placenta of preeclampsia patients (van Dijk et al., 2005). Likewise, expression of the mutant protein inhibits trophoblasts invasion *in vitro*, suggesting a possible mechanism by which STOX1 mutation could have a role in the development of preeclampsia. Finally, a recent report from Doridot et al. demonstrated that transgenic overexpression of STOX1 in the mouse leads to a phenotype that mimics preeclampsia in several key ways, most notably a dramatic rise in systolic blood pressure during gestation (See Figure 2) and elevated maternal circulating levels of sFlt-1 and soluble endoglin (Doridot et al., 2013). While these data are intriguing, much work remains to be done to elucidate the causative and symptomatic role of STOX1 in the development of preeclampsia.

Recent studies have also suggested that variability of immune system genes that code for major histocompatibility complex molecules and natural killer receptors may also impact human placentation (Colucci et al., 2011). These studies reported that specific combinations of fetal major histocompatibility complex molecules and maternal natural killer receptor genes in humans correlate with the risk of preeclampsia, recurrent miscarriage, and fetal growth restriction. Researchers have begun to explore the similarities and differences between human and mouse natural killer cells and potential trophoblast ligands with the aim of developing mouse models to elucidate how natural killer cell–trophoblast interactions contribute to placentation.

Activation and Dysfunction of the Endothelium in Preeclampsia

The maternal vascular endothelium of women destined to develop preeclampsia appears to be an important target of factors that are presumably generated through placental hypoxia/ischemia (Gilbert et al., 2008, Krauss et al., 1997, LaMarca et al., 2008b, Roberts and Gammill, 2005, Roberts et al., 1991). The vascular endothelium has many important properties including control of smooth muscle tone through release of vasoconstrictor and vasodilatory substances, and regulation of anti-coagulation, anti-platelet, and fibrinolysis functions via release of different soluble factors. Alterations in the circulating levels of many markers of endothelial dysfunction have been reported in women that develop preeclampsia (Gilbert et al., 2008, Krauss et al., 1997, LaMarca et al., 2008b, Roberts and Gammill, 2005, Roberts et al., 1991). The fact that endothelial dysfunction can be demonstrated prior to overt disease, supports a causal role.

Maternal status may influence the endothelial response to factors triggered by placental ischemia/hypoxia in preeclampsia. There is compelling evidence, for example, that obesity, a major epidemic in developed countries including the U.S. increases the risk of preeclampsia. A high body mass index, for example, increases this risk three-fold (Roberts et al., 2011). Despite this and many other studies linking obesity to preeclampsia, the pathophysiological mechanisms whereby obesity increases the risk for developing preeclampsia are unclear. Thus, further research into how obesity and metabolic factors such as leptin, insulin, and free fatty acids impact the various stages of preeclampsia is warranted.

Factors Linking Placental Ischemia/Hypoxia with the Microvascular Dysfunction and Hypertension

Angiogenic Factors

In response to placental hypoxia, the placenta is proposed to produce pathogenic factors, which enter the maternal blood stream and are responsible for the endothelial dysfunction and other clinical manifestations of the disorder including hypertension and proteinuria. A variety of molecules are released but amongst them, anti-angiogenic and autoimmune/inflammatory factors have received the greatest attention (Gilbert et al., 2008, LaMarca et al., 2008b, Mutter and Karumanchi, 2008, Wang et al., 2009). One of the most intensely studied pathways in the manifestation of preeclampsia is that related to vascular endothelial growth factor (VEGF) signaling. VEGF and the placental growth factor (PlGF), besides their role in angiogenesis are also important in the maintenance of proper endothelial cell function and health (Gilbert et al., 2008, LaMarca et al., 2008b, Mutter and Karumanchi, 2008, Wang et al., 2009). This signaling pathway came to prominence with the discovery of elevated circulating and placental levels of the soluble form of the VEGF receptor, fms-related tyrosine kinases (sFlt)-1. sFlt-1 is a circulating soluble receptor for both VEGF and PlGF, which when increased in maternal plasma leads to less circulating free VEGF and free PlGF, thus preventing their availability to stimulate angiogenesis and maintain endothelial integrity. In the kidney this inactivation of free VEGF is believed to cause endotheliosis and proteinuria (Mutter and Karumanchi, 2008, Wang et al., 2009). Subsequent studies of the regulation of sFlt-1 in cell culture and placental tissue *in vitro* have demonstrated that sFlt-1 is released from placental villi and trophoblast cells in response to reduced oxygen tensions similar to that seen in an ischemic placenta (Gilbert et al., 2008, Mutter and Karumanchi, 2008, Wang et al., 2009). While sFlt-1 production appears to be regulated by the hypoxia inducible factor-1, other factors such as tumor necrosis factor (TNF)- α and the agonistic autoantibody to the angiotensin II type I receptor (AT1-AA) also appear to be involved.

Several lines of evidence support a role for angiogenic factors in the pathogenesis of preeclampsia. sFlt-1 levels are strongly correlated with the severity of the syndrome (Levine et al., 2004, Mutter and Karumanchi, 2008, Wang et al., 2009). In addition, chronic administration of sFlt-1 to pregnant rats, to mimic plasma concentrations observed in preeclamptic women, decreases free VEGF and PlGF and produces hypertension and proteinuria (Gilbert et al., 2008, LaMarca et al., 2008b, Maynard et al., 2003). Likewise, VEGF transgenic overexpression or knockout in mouse glomerular podocytes resulted in proteinuria and glomerular endotheliosis, two common preeclamptic features (Eremina et al., 2003). Similar findings are observed in cancer patients who have been treated with VEGF monoclonal antibodies, as hypertension and proteinuria are common side effects (Zhu et al., 2007). Moreover, a promising pilot study recently demonstrated that sFlt-1 could be removed from the maternal circulation of preeclamptic women by apheresis safely, and that this therapy reduced both blood pressure and proteinuria, with a trend toward increased gestational duration (Thadhani et al., 2011).

While compelling data derived from animal and human studies suggest an important role for angiogenic imbalance in the pathophysiology of preeclampsia, there are many unanswered questions and many opportunities for future research. For example, the molecular mechanisms involved in the regulation of sFlt-1 production have yet to be fully elucidated. Moreover, while sFlt-1 appears to play an important role in the pathogenesis of preeclampsia, specific inhibitors of sFlt-1 production are not currently available. Thus, research into the discovery of inhibitors of sFlt-1, or ways to stimulate greater production of VEGF and PlGF is of critical importance.

Immune factors and Inflammation

One of the earliest and most persistent theories about the origins of preeclampsia is that preeclampsia is a disorder of immunity and inflammation. Of interest is work suggesting that the inflammatory response is triggered by particles, ranging from large deported multinuclear fragments to sub-cellular components, shed from the syncytial surface of the human placenta. These circulating particles are increased in preeclampsia. In this respect, Redman and colleagues proposed that the fragments include pro-inflammatory proteins that may contribute to the systemic inflammatory response in normal pregnancy and the exaggerated inflammatory response in preeclampsia (Germain et al., 2007). There is newer evidence from Redman and colleagues of a large 'hidden' population of microvesicles and nanovesicles (including exosomes), not easily studied because of their small size (Redman et al., 2012). Utilizing nanoparticle tracking analysis to measure the size and concentration of syncytiotrophoblast vesicles obtained by placental perfusion they found that vesicles range in size from 50 nm to 1 μ m with the majority being <500 nm (which includes both exosomes and microvesicles). The authors speculated that changes in the numbers and size of beneficial syncytiotrophoblast exosomes and harmful microvesicles may be important in the maternal syndrome of preeclampsia.

Maternal immune tolerance mechanisms are also implicated in the pathophysiology of preeclampsia (Redman and Sargent, 2010). This maternal immune tolerance involves crucial interactions between regulatory CD4 + T cells and uterine natural killer cells recognizing and accepting the fetal antigens and facilitating placental growth. Complete failure leads to spontaneous miscarriage while partial failure of this crucial step leads to poor placentation and dysfunctional placental perfusion and chronic immune activation originating from the placenta. Preeclamptic women have a decrease in circulating regulatory CD4 + T cells (Prins et al., 2009). Moreover, placental ischemic rats have a 47% decrease in regulatory CD4 + T cells in the peripheral circulation when compared to normal pregnant rats (Wallace et al., 2011). T helper 17 cells, which are upregulated in a variety of autoimmune disorders, are also increased in preeclamptic women and in placental ischemic rats (Wallace et al., 2011). While these data support the hypothesis that hypertension in response to placental ischemia represents a shift from the normal anti-inflammatory state of pregnancy to a pro-inflammatory state, the quantitative importance of CD4 + T cells and T helper 17 cells in the pathophysiology of preeclampsia remains to be determined.

Another area related to the immune component of preeclampsia is research on the agonistic autoantibodies to the angiotensin Type 1 receptor (AT1-AA). While various components of the classical renin-angiotensin system are suppressed in preeclampsia, women with preeclampsia produce a novel agonistic autoantibody to the angiotensin II type I receptor (Herse et al., 2008, Irani and Xia, 2011, LaMarca et al., 2012). Dechend and colleagues previously reported that sera from preeclamptic women contain an IgG (type 3) autoantibody that reacts with the AT1 receptor (Wallukat et al., 1999). The binding of the AT1-AA to the seven amino acid stretch of the second extracellular loop of the angiotensin II type 1 receptor stimulates a chronotropic response from rat neonatal cardiomyocytes which can be attenuated with administration of an AT1 receptor antagonist, which is the

basis of the bioassay primarily used for the detection of the autoantibody (Wallukat et al., 1999). These autoantibodies, isolated over a decade ago in preeclamptic women, have been studied more intensively recently, including their identification in the circulation of rats undergoing placental ischemia (LaMarca et al., 2008a). Interestingly, these autoantibodies appear to be induced by the production of the cytokine, TNF- α . Indeed, infusion of TNF- α to pregnant rats results in the production of the autoantibody to levels comparable to the levels observed in pregnant women with preeclampsia and placental ischemic rat (LaMarca et al., 2008a). It has also been demonstrated that infusion of affinity-purified AT1-AA directly into pregnant rats results in moderate hypertension that is associated with increases in plasma sFtl-1 and reactive oxygen species (Parrish et al., 2010, Parrish et al., 2011, Zhou et al., 2008). However, the pathogenic importance of these antibodies remains to be fully elucidated, as their presence has been noted post-partum in a subset of preeclamptic patients even after the symptoms were resolved. Further studies are needed including determining how these unique antibodies are produced and how they interact with the other pathogenic agents in preeclampsia to produce the clinical phenotype.

Endothelin

There is growing evidence to suggest an important role for endothelin-1 (ET-1) in the pathophysiology of preeclampsia. First characterized over twenty years ago, ET-1 was identified as a potent endothelium-derived vasoconstrictor, the most potent vasoconstrictor known. Derived from a longer 203-amino acid precursor known as preproendothelin, the active peptide is proteolytically cleaved into its final 21-amino acid form. Much of the research on endothelin-1 has focused on the role of the endothelin type A (ET_A) receptor in the vascular smooth muscle and how they serve as important regulators of ET-1 dependent vasoconstriction and cellular proliferation.

Multiple studies have examined circulating levels of ET-1 in normal pregnant and preeclamptic cohorts, and found elevated levels of plasma ET-1 in the preeclamptic group, with some studies indicating that the level of circulating ET-1 correlates with the severity of the disease symptoms, though this is not a universal finding (Benigni et al., 1992, George and Granger, 2011, Mastrogiannis et al., 1991, Taylor et al., 1990). ET-1, however, is produced locally and plasma levels typically do not reflect tissue levels of the peptide. Animal studies have shown that a myriad of experimental models of preeclampsia (placental ischemia, sFtl-1 infusion, TNF- α infusion, and AT1-AA infusion) are associated with elevated tissue levels of ET-1 (Alexander et al., 2001, LaMarca et al., 2009, LaMarca et al., 2005, Murphy et al., 2010) (See Figure 3). A recent report also indicated increased vascular contractility to big ET-1 in the reduced uteroplacental perfusion pressure model of preeclampsia, an effect that was attributed to a greater contribution of matrix metalloproteinases to cleavage of bET-1 to ET-1 (Abdolvand et al., 2013, Palei et al., 2013). Finally, the fact that hypertension in pregnant rats, induced by placental ischemia or chronic infusion of sFtl-1, TNF- α , or AT1-AA can be completely attenuated by ET_A receptor antagonism, strongly suggests that ET-1 appears to be a final common pathway linking factors produced during placental ischemia to elevations in blood pressure (George and Granger, 2011).

Recent studies in animal models suggest the ET-1 system be a potential therapeutic target for the treatment of preeclampsia. Since there is evidence that interfering with the ET_A receptor in early animal pregnancy may abort the pregnancy or lead to developmental anomalies, future research should focus later in gestation where ET_A receptor antagonists might prove safe and efficacious, during the symptomatic phase of the disease. Alternatively, development of ET_A receptor antagonists that do not cross the placental barrier would be welcome, and indeed, Thaete and colleagues recently reported that a

selective ET receptor antagonist had limited access to the fetal compartment during chronic maternal administration late in pregnancy (Thaete et al., 2012).

Nitric oxide

Studies have suggested an important role for nitric oxide (NO) in modulating arterial pressure under various physiological and pathophysiological conditions (Gilbert et al., 2008, LaMarca et al., 2008b). NO is synthesized endogenously from L-arginine, oxygen, and NADPH by various NO synthase enzymes. NO production is elevated in normal pregnancy and these increments appear to play an important role in the vasodilatation that occurs in pregnancy (Conrad et al., 1999, Davidge et al., 1996). Thus, it was postulated that NO deficiency during preeclampsia might be involved in the disease process. Whether there is a reduction in NO production during preeclampsia is controversial. Much of the uncertainty originates from the difficulty in directly assessing the activity of the NO system in a clinical setting. Assessment of whole body nitric oxide production via measurement of 24-hour nitrate/nitrite excretion has yielded variable results, likely due to difficulties in controlling for factors such as nitrate intake and excretion. Thus, the relative importance of NO deficiency in the pathogenesis of preeclampsia has yet to be fully elucidated.

In support of a role for NO deficiency in the pathogenesis of preeclampsia are reports from several laboratories that chronic NOS inhibition in pregnant rats produces hypertension associated with peripheral and renal vasoconstriction, proteinuria, intrauterine growth restriction, and increased fetal morbidity, a pattern resembling the findings of preeclampsia (Deng et al., 1996, Gilbert et al., 2008, LaMarca et al., 2008b). Placental ischemia has been reported to result in endothelial dysfunction and reduced NO production in some but not all vascular beds. Moreover, L-arginine supplementation in animal models and in women with preeclampsia has been reported to reduce blood pressure and improve pregnancy outcomes in some but not all studies (Alexander et al., 2004, Gilbert et al., 2008, LaMarca et al., 2008b).

Oxidative and Endoplasmic Reticulum Stress

Oxidative stress has also been implicated in preeclampsia, as increased concentration of several oxidative stress markers have been reported systemically in preeclamptic women, among these peroxynitrite (Hung and Burton, 2006, Roggensack et al., 1999, Walsh, 1998). Peroxynitrite concentrations in vascular endothelium were much higher in preeclamptic women versus normal gestation, concurrent with decreased levels of superoxide dismutase (SOD) and nitric oxide synthase (Hung and Burton, 2006, Roggensack et al., 1999, Walsh, 1998). There is also evidence of increased oxidative stress during gestation in the placental ischemic rat hypertensive model, suggesting a link between placental ischemia/hypoxia and the production of reactive oxygen species (Gilbert et al., 2008, LaMarca et al., 2008b, Sedeek et al., 2008). The SOD mimetic drug Tempol, however, led to significant attenuation of the hypertensive response. In a related study, administration of the NADPH Oxidase inhibitor apocynin also significantly attenuated placental ischemia-induced gestational hypertension, implicating the enzyme as an important source of pathogenic ROS in the RUPP animal (Gilbert et al., 2008, LaMarca et al., 2008b). Failure of the drug to fully normalize blood pressure, however, leaves open the possibility that alternative ROS production pathways are at work in the RUPP model. Further studies into the mechanism of ROS production in animal models of preeclampsia should help shed light into the importance of oxidative stress in the pathophysiology of preeclampsia and perhaps allow the identification of useful antioxidant strategies. It remains to be seen whether ROS production is a primary or secondary cause of preeclampsia pathophysiology, and how effective manipulation of the system will be in the search for effective therapies.

There also appears to be an excess of endoplasmic reticulum stress in placentas from women with early-onset preeclampsia (Burton and Yung, 2011). Endoplasmic reticulum stress activates a number of signaling pathways aimed at restoring homeostasis. Burton and colleagues proposed that this mechanism to restore homeostasis fails and apoptotic pathways are activated to alter placental function in women who develop preeclampsia (Burton and Yung, 2011). In addition chronic, low levels of endoplasmic reticulum stress during the second and third trimesters may result in a growth restricted phenotype. They also propose that higher levels of endoplasmic reticulum stress lead to activation of pro-inflammatory pathways that may contribute to maternal endothelial cell activation (Burton and Yung, 2011). While endoplasmic reticulum stress is known to occur in preeclampsia, the importance of this abnormality in the pathophysiology has yet to be fully elucidated.

Hemeoxygenase

The stress response gene heme oxygenase-1 (HO-1) and its catalytic product, carbon monoxide (CO) have also been implicated in the pathogenesis of preeclampsia (Cao et al., 2009). In support of this concept, there is a study demonstrating that genetic or pharmacological blockade of HO-1 in pregnant animals lead to preeclampsia like phenotypes (Zhao et al., 2009). However, the effects of HO inhibition are on blood pressure and proteinuria are modest.

There are also several lines of evidence that HO-1 and its catalytic products may protect against the progression of preeclampsia by interfering at several sites in the pathway that links placental hypoxia and hypertension. For example, TNF- α mediated cellular damage in placental villous explants can be prevented by up-regulating HO enzyme activity (Ahmed et al., 2000). HO products have also been shown to inhibit the release of sFlt-1 in several *in vitro* models (Cudmore et al., 2007, George et al., 2012). Induction of the HO-1 enzyme or chronic administration of HO-1 metabolites have also been reported to ameliorate hypertension in several animal models of hypertension that involve blood pressure regulatory factors similar to that observed in preeclamptic women (Wang et al., 2006). More compelling evidence that supports the concept that HO-1 and/or its catalytic products may protect against the progression of preeclampsia are data indicating that chronic administration of an HO-1 enzyme inducer, CoPP, or a CO releasing molecule, CORM-A1, significantly attenuates hypertension in response to placental ischemia (George et al., 2011). Taken together, these findings make HO a potential target for studies to improve the treatment of preeclampsia (Ahmed and Cudmore, 2009).

Summary

Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia has yet to be fully elucidated. However, it is evident that this disorder is complex and involves multiple organ systems, and by using integrative approaches, enormous progress has been made towards understanding the pathophysiology of preeclampsia during the past decade. Growing evidence support the concept that the placenta plays a central role in the pathogenesis of preeclampsia and that reduced uteroplacental perfusion which develops as a result of abnormal cytotrophoblast invasion of spiral arterioles triggers the cascade of events leading to the maternal disorder. Placental ischemia is thought to lead to widespread activation/dysfunction of the maternal vascular endothelium that results in enhanced formation of endothelin and superoxide, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide. These endothelial abnormalities, in turn, cause hypertension by impairing renal-pressure natriuresis and increasing total peripheral resistance (**Summarized in figure 4**).

While recent studies support a role for angiogenic factors, AT1-AA, cytokines, and other factors as potential mediators of endothelial dysfunction, finding the link between placental ischemia and maternal endothelial and vascular abnormalities remains an important area of investigation. Microarray analysis of genes and microRNAs within the ischemic/hypoxic placenta of women with preeclampsia and in animal models of placental ischemia should provide new insights into novel factors that may provide additional links between placental ischemia/hypoxia and hypertension. The full elucidation of the molecular and cellular mechanisms involved in various stages of the disease process will hopefully lead to a more complete understanding of the etiology of preeclampsia and eventually lead to successful therapeutic intervention through the targeted disruption of new and novel pathways.

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Figure 1.

Vascular corrosion casting was used to examine maternal blood spaces of the placenta from mice at embryonic (E) days 10.5 and 14.5. The trophoblast cell-lined vascular canals supplying blood to the placenta were smaller from Notch2 knockout (KO) compared to wild type (WT) rats at both embryonic days. These data indicate that Notch2 is important for proper remodeling of the placental vasculature. Figure adapted from Hunkapiller et al., 2011.

Figure 2.

Systolic blood pressure in wild type (WT) female rats mated with transgenic male mice overexpressing the STOX13, one of the transgenic lines generated to overexpress the transcription factor STOX1, or male WT mice. This mating strategy resulted in pregnant female having placentas overexpressing or having normal expression of STOX1, respectively. Female mice with overexpression of placental STOX1 developed a progressive hypertensive phenotype that subsided after parturition. Figure adapted from Doridot et al., 2013.

Figure 3.

Renal cortical mRNA expression of preproET-1 in normal pregnant (NP) rats infused with sFlt-1 from embryonic days 14-19 (A) and mean arterial blood pressure (MAP) in NP rats infused with sFlt-1 co-treated with or without the ET_A receptor antagonistic ABT-627 (B). sFlt-1-induced hypertension was linked to greater renal expression of ET-1 and the blood pressure response was dependent ET-1. Figure adapted from Murphy et al., 2010.

Figure 4.

Hypothetical scheme depicting how abnormal cytotrophoblast invasion and subsequent reductions in spiral artery remodeling results in endothelial dysfunction and hypertension in preeclampsia.