The heme oxygenases: important regulators of pregnancy and preeclampsia

Eric M. George,1,2 Junie P. Warrington,1 Frank T. Spradley,1 Ana C. Palei,1 and Joey P. Granger1

1Department of Physiology and Biophysics, The University of Mississippi Medical Center, Jackson, Mississippi; and 2Department of Biochemistry, The University of Mississippi Medical Center, Jackson, Mississippi

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George EM, Warrington JP, Spradley FT, Palei AC, Granger JP. The heme oxygenases: important regulators of pregnancy and preeclampsia. Am J Physiol Regul Integr Comp Physiol 307: R769–R777, 2014. First published June 4, 2014; doi:10.1152/ajpregu.00132.2014.—The heme oxygenase system has long been recognized as an integral component of the cellular stress response. It serves to limit the toxicity of the prooxidant heme molecule by converting it to the less-problematic bilirubin molecule. In the course of this reaction, several biologically active molecules are also produced: CO, bilirubin, and iron. The heme oxygenases are enigmatic enzymes, responsible for their own production and for the production of their products. While the biological activities of the CO and bilirubin products are well known, the iron product has been somewhat neglected. In this review, it will be apparent that the heme oxygenases and their products have a significant impact on both healthy and pathological physiological states. The heme oxygenases and their products have been shown to have a significant impact on cardiovascular function and may have significant impact on the pathogenesis of preeclampsia.

ONE OF THE MOST ELEGANTLY orchestrated physiological processes in humans is maternal cardiovascular adaptation to pregnancy, and the associated growth and development of the fetus and placenta during pregnancy. As the fetus develops, it requires a concurrent increase in blood supply to the placenta for adequate oxygen and nutrient transfer. To provide this increased nutrient delivery, the placenta and maternal vasculature that supply it must undergo significant development and adaptation. In particular, fetally derived cells must invade and remodel the maternal vessels to allow for more vascular capacity. While this pivotal process typically proceeds without a problem, it has become recognized that in some cases, some, yet unknown, molecular defects block these maternal adaptations, leading to placental underperfusion. This, in turn, is believed to underlie a significant proportion of obstetrical complications, preeclampsia, and fetal growth restriction.

The molecular cues that are necessary for these adaptations and the response of the placenta to this hypoperfusion are still poorly understood and are areas of active investigation. One molecule that has been strongly implicated in both the normal development of the uteroplacental circulation and in the ischemic stress response, in the case of defective remodeling, is the stress-response protein heme oxygenase.

Long known to be an important “housekeeping” protein responsible for the breakdown of free heme derived from the degradation of heme-containing proteins, the importance of heme oxygenase in both normal cellular physiology and the cellular stress response has come to be appreciated in the recent decades (31). Heme oxygenase exists as two primary isoforms, heme oxygenase-1 (HO-1) and heme oxygenase-2 (HO-2), originating from nonallelic homologous genes. HO-2 is generally believed to be constitutively expressed, while HO-1 is readily inducible by multiple mechanisms. Both enzymes readily catalyze the prooxidant heme into the antioxidant biliverdin, the rate-limiting step into its final conversion to bilirubin by biliverdin reductase (Fig. 1). As a result of this conversion, not only is the oxidant heme neutralized, but three bioactive metabolites (elemental iron, CO, and bilirubin itself) are formed, which have all been shown to have distinct physiological functions. CO, for instance, is a potent vasodilator with activity similar to nitric oxide and has been implicated in both regulation of angiogenic factors and maintenance of vascular tone (14, 17, 23, 32, 70, 73). Although ultimately conjugated and excreted as a waste product, bilirubin also seems to function as a powerful antioxidant in a number of systems, as has the intermediate molecule biliverdin (42, 44, 45, 60). It should be noted, however, that the precise mechanisms by which these molecules act is still a matter of debate, and there are several unresolved controversies which are beyond the scope of this review (28). The free elemental iron is a potent prooxidant molecule. However, increase in intercellular iron produces increased production of the protein ferritin, which scavenges iron, leading to a net decrease in free iron and overall decrease in oxidant status (19). As cardiovascular disease frequently involves impaired vascular reactivity and increased oxidative stress, each of these molecules has the potential to directly affect the cardiovascular system in both healthy and pathophysiological states, and the induction of HO-1 to increase the levels of its metabolites for the treatment
of cardiovascular disease is an area of active research (9, 10, 12, 49, 51, 64, 65, 71). It is logical then, that preeclampsia, which shares many common pathological molecular pathways with other forms of cardiovascular disease, might also be therapeutically targeted by induction of heme oxygenase or its individual metabolites. What has only become apparent in recent years, however, is the important role of the heme oxygenase system in the establishment and maintenance of healthy pregnancy. This review will summarize recent data that implicate the heme oxygenase system as a key regulator of placental development and pregnancy maintenance, as well as studies that have hinted that manipulation of the heme oxygenase system could serve as a valuable therapeutic approach for the management of the preeclampsia patient.

**Role of Heme Oxygenases in Placental Development**

One of the most important processes for the completion of a successful pregnancy is the formation of the placenta to allow for adequate maternal and fetal blood flow, promoting the exchange of nutrients and metabolic waste products between the two circulations. Just as important, the placenta acts as an extremely selective exchange site, allowing for the exchange of the necessary metabolic factors while virtually excluding free passage of cells and larger proteins. Besides the formation of the organ itself, significant remodeling of the maternal uterine vasculature that perfuses the placenta, specifically the spiral arteries, is necessary. This is accomplished by placental extravillous trophoblasts, which migrate into the spiral arteries and replace the vascular endothelial cells. In the process, the arteries become grossly distended, with significantly higher capacitance and lower resistance (48). The effects of this remodeling can be seen by the change in placental Po2 through gestation. At 7–10 wk of gestation, the Po2 of the placenta is ~25 mmHg, but increases dramatically to ~55 mmHg at 11–16 wk of development, a level that is maintained through the second trimester. However, the placental Po2 is still significantly lower than that seen in the surrounding uterine tissue, making the placenta slightly hypoxic, even in a healthy pregnancy (29, 57).

While a great deal is known about the development of the placenta, especially from an anatomical and developmental perspective, the molecular regulation of placental development and its remodeling of the maternal uterine vasculature remains largely obscure. Intriguingly, there have been several recent reports that suggest that heme oxygenases may play an important role in some of these poorly understood aspects of placental development. In normal human pregnancies, the placenta expresses significant amounts of both HO-1 and HO-2, which is not surprising. What is intriguing is that there appears to be a greater increase in the HO-2 isoform than the HO-1 isoform (7, 38, 46, 72). This is slightly counterintuitive, as the HO-1 isoform is known to be induced by hypoxia, among other factors, while the HO-2 isoform is typically described as a constitutively expressed housekeeping gene. Likewise, in mice, HO-1 expression in the placenta increases steadily through the second trimester before steadily declining until term, a pattern that is directly correlated to the level of placental tissue oxygenation, which increases to midgestation before gradually declining until term (30, 68).

### Fig. 1. Heme oxygenases catalyze the rate-limiting step in the conversion of free heme to bilirubin. Oxidation of free heme produces biliverdin, free iron, and carbon monoxide. Biliverdin is rapidly converted to bilirubin by biliverdin reductase. HO, heme oxygenase; BVR, biliverdin reductase.
in the remodeling of the maternal vasculature during placental development remains a subject of considerable interest and provides fertile ground for future studies.

These in vitro studies suggesting a role for heme oxygenases in placental development have recently received some support from a series of in vivo studies utilizing transgenic manipulation of HO-1. Initial attempts to generate HO-1-null mutant mice were complicated by a dramatically lower survival rate for the homozygous knockout offspring than would be predicted by Mendelian chance, with less than 3% of the knockout animals surviving successfully to term. Furthermore, the litters generated by crossing of HO-1+/− mice were shown to have both reduction in fetal weight and litter size. Importantly, it was not simple embryonic lethality that caused this phenotype, but the lack of HO-1 production resulted in distinct morphological changes in placental structure, specifically thinning of the junctional zone. It is important to note that the decrease in HO-1 was accompanied by a concomitant increase in HO-2 production, leading to a net heme oxygenase activity that did not differ significantly from control animals, implying that overall heme oxygenase activity is not the factor driving these changes in placental remodeling and giving further support to the idea that the two isoforms are functionally distinct (81).

However, it cannot be ruled out that differences of expression in specific cellular populations may also play a role. In a related study, Zenclussen et al. (78) studied crosses of HO-1 heterozygous knockouts and found that within litters, fetal loss was increased in HO-1+/− offspring, and greatly increased in HO-1−/− fetuses. They also found that HO-1-deficient fetuses had defective blastocyst attachment to the uterine wall and greater placental fibrosis. Promisingly, these phenotypes could be significantly attenuated by exposure of the mother to low-dose inhaled carbon monoxide, implicating CO as the key molecular mediator of HO-1’s protective actions during pregnancy (78).

In addition to its actions on placental structure, HO-1 has also been shown to affect maternal vascular remodeling in vivo. Zhao et al. (80) recently examined the placental/uterine vascular structure of HO-1+/− mice using three-dimensional microcomputerized tomography coupled to vascular corrosion casting. Regardless of HO-1 phenotype, all of the offspring exhibited deficiency in spiral artery remodeling and defects in the fetal capillaries and sinusoid spaces of the placental labyrinth, the region of the maternal fetal interface. This was associated with significant changes in the production of angiogenic factors by the placenta as determined by PCR array (80). That these changes were seen independently of fetal HO-1 status suggests that maternally derived HO-1 is also an important factor in successful gestational outcome. Recently, Linzke et al. (36) demonstrated that HO-1 deficiency is associated with reduced uterine natural killer (uNK) cells and their associated angiogenic factors. As a result, maternal spiral artery remodeling was significantly inhibited. Surprisingly as seen in Fig. 2, administration of low-dose CO through early gestation resulted in a restoration of uNK cell levels and improved remodeling of the spiral arteries. Together, these studies strongly suggest that

![Fig. 2. Inhalation of carbon monoxide (CO) attenuated the placental defects seen in heme oxygenase-1+−/− (HO-1+−/−) mice. A: Dolichus biflorus agglutin staining of gestational day 10 implantation sites from HO-1-deficient mice given air or 50 ppm CO from gestational day 3–8 is shown. Uterine natural killer cells were significantly increased in animals subjected to CO inhalation (B). Likewise, spiral artery remodeling was significantly improved with CO inhalation, which is readily apparent (C). Quantitatively, this resulted in ~30% reduction of the wall-to-lumen-diameter ratio (D). [Adapted with permission Lippincott Williams and Wilkins/Wolters Kluwer Health. Hypertension 63: 580–588, 2014 (From Ref. 36)].](http://ajpregu.physiology.org/doi/10.1152/ajpregu.00132.2014)
HO is involved in the arterial remodeling, which takes place during the establishment of placental perfusion.

**Heme Oxygenases in the Maternal Adaptations to Pregnancy**

A myriad of maternal adaptations are necessary for the maintenance of a healthy pregnancy, including a number of cardiovascular, immunoregulatory, and hemodynamic changes. In addition, the uterine bed must remain quiescent during pregnancy to prevent spontaneous abortion. Several recent studies suggest a role for heme oxygenases in these adaptations. Acevedo et al. first reported that induction of heme oxygenase by the porphyrin hemin could decrease oxytocin-induced contractility in human myometrial blood vessels (1). From the perspective of the fetal circulation, Bainbridge et al. (6) utilized isolated placental perfusion techniques to examine the role of carbon monoxide in the regulation of fetal vascular function. Interestingly, when the fetal circulation was preconstricted, the addition of CO to the perfusate of the maternal side significantly decreased the fetal circulation perfusion pressure, an indicator of vascular resistance. This effect was also shown to be dependent on soluble guanylyl cyclase (sGC), as the effect could be inhibited by a sGC antagonist and augmented with a sGC activator. Maternal/placental production of CO could be acting directly during pregnancy to vasodilate fetal vessels and maintain blood flow through the placenta.

Alterations in the heme oxygenases have also been linked repeatedly to spontaneous abortion. This was first reported in an abortion-prone mouse model, in which stress or IL-12-induced abortion was associated with decreased placental expression of both HO-1 and HO-2 (74). Subsequent studies in spontaneous idiopathic abortion in humans also demonstrated a significantly decreased expression of HO-2 in both early and late abortions, specifically in the trophoblasts and syncytiotrophoblasts, and a trend for decreased HO-1, which did not reach significance (75). It has also been shown that a microsatellite polymorphism in the HO-1 gene is associated with the occurrence of idiopathic recurrent miscarriage (16). Furthermore, induction of HO-1 has been shown to be protective in the *Brucella abortus* and *Listeria monocytogenes*-induced abortion murine models. Interestingly, both infections were shown to significantly downregulate HO-1 expression in the placenta. Chemical induction of HO-1 subsequently increased fetal survival and was shown to be cytoprotective in the placental tissue itself (61, 62).

A number of innate and adaptive immune mechanisms are important in the development of pregnancy, which are beyond the scope of this article (see Refs. 73 and 13 for a detailed review), and dysregulation of the immune response is believed to underlie a significant portion of spontaneous abortions. Recent evidence supports a role for HO-1 in modulating the maternal immune response during pregnancy in animal models, in particular, a series of studies from the Zenclussen lab group. Early observations demonstrated that ectopic expression of HO-1 was protective in an abortion-prone mouse model (77). This was shown to be associated with increased levels of the antiapoptotic protein Bag-1 and the T-regulatory cell marker neuropilin-1, from which the authors concluded that HO-1 could be increasing maternal/fetal tolerance and, therefore, reducing the incidence of miscarriage (56). The interplay of HO-1 and Bag-1 was also examined in clinical samples, where trophoblasts from spontaneous abortions were shown to have decreased HO-1 and Bag-1 compared with trophoblasts from healthy pregnancies. When pregnant HO-1+/- mice were challenged with LPS, a significant decrease in Bag-1 expression was observed in the placenta compared with HO-1+/- mice, suggesting that HO-1 is cytoprotective in the placenta during an inflammatory challenge by upregulation of Bag-1 (33). Finally, blockade of HO-1 attenuated the protective effects of adoptive T-reg cell transfer in a mouse model of spontaneous abortion, an effect associated with aberrant dendritic cell maturation. This indicates that HO is essential for maintenance of an immature dendritic cell pool. As it has been shown that dendritic cells are important for the proliferation of T-reg cell expansion and T-reg cells are crucial for the suppression of auto-immune response, this is likely to be an important process in promoting fetal tolerance and preventing rejection of the developing placenta and fetus (53, 82). These data strongly suggest that heme oxygenases play an important role in modulating the maternal adaptive and innate immune responses during pregnancy and help establish maternal tolerance of the fetus.

**Heme Oxygenases in the Development and Treatment of Preeclampsia**

One of the most prevalent obstetrical disorders worldwide is preeclampsia, which affects ~8% of all pregnancies in the United States, and is a leading cause of perinatal mortality (50). Preeclampsia is most prominently associated with new-onset hypertension, typically after the 20th wk of gestation, often accompanied by proteinuria (4). There are currently few treatment options for the management of the preeclampsia patient, typically magnesium sulfate for seizure prophylaxis and anti-hypertensive drugs to limit the associated hypertension. Ultimately, the disease only remits after parturition. Therefore, induction of labor, often preterm, is indicated in severe cases, making preeclampsia a leading cause of premature births (63). While the underlying etiology of the disease is still in debate, a clue to the origins of the disease symptoms comes from the observation that remission only occurs with delivery of the placenta and that delivery of the fetus alone is insufficient (27, 54). A host of evidence now indicates that in preeclampsia patients, inadequate remodeling of the spiral arteries leads to placental hypoperfusion and chronic ischemia. In turn, the ischemic placenta responds by releasing factors into the maternal bloodstream, resulting in systemic maternal endothelial dysfunction and hypertension (11, 25, 34). Among several factors believed to be important in the symptomatic phase of the disorder are placental production of the antiangiogenic protein soluble fms-like tyrosine kinase-1 (sFlt-1), inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), and increased oxidative stress (39, 52, 58, 59). As indicated above, heme oxygenases have been implicated as players in the remodeling of the spiral arteries in animal models, it is, therefore, possible that alterations in the heme oxygenases could be responsible for the failure of these vessels to remodel and, therefore, cause placental ischemia-induced hypertension in the preeclampsia patient. Indeed, in the studies of pregnancy in the HO-1+/- mouse, Zhao et al. (81) found that in addition to the defects in vascular remodeling discussed above, the maternal diastolic blood pressure of these animals was mildly...
but significantly elevated, as was the circulating level of sFlt-1. More recently, we demonstrated that pharmacological inhibition of HO-1 only in late pregnancy also caused a significant increase in mean blood pressure, and it was associated with decreased vascular endothelial growth factor (VEGF) production by the placenta and significant elevations in the activity of placental NADPH oxidase, a major source of superoxide (24).

From a clinical standpoint, reports from various groups have indicated alterations in heme oxygenases in preeclampsia patients, although the findings have yet to form a clear phenotypic pattern. Initial studies looking at both HO-1 and HO-2 in the placenta found little change globally, but significant decreases in HO-2 expression in placental endothelial cells, again challenging the notion that HO-2 is a constitutively expressed isoform with little inducible regulation (7). Subsequent studies from a separate group found a similar pattern of decreased expression and also noted that HO-2 levels were decreased in syncytiotrophoblasts (55). Finally, a recent report again found a decrease in syncytiotrophoblasts and additionally found that invasive trophoblasts also had decreased HO-2 (75). Together, with previously mentioned studies showing a role for HO-2 in vascular remodeling (38, 41), these data support the idea that a reduction in trophoblasts’ invasive potential in the preeclampsia patient is associated with decreased expression of HO-2 at the maternal-placental interface.

The HO-1 isoform has also been shown to be altered in preeclampsia patients. Targeted studies in the decidua basalis found significant increases in the levels of HO-1 in placentas from preeclampsia patients compared with healthy controls. This was accompanied by an increase in circulating levels of HO-1 in the maternal serum, although whether the circulating protein originated from the placenta is not clear (18). Interestingly, a subsequent study from Vitoratos et al. (66) confirmed that serum circulating HO-1 was increased in severe preeclampsia patients compared with mild cases and healthy pregnancies, but that HO-1 decreased significantly in healthy patients only immediately post-partum, while it remained significantly elevated in all preeclampsia patients. Further, they found that the level of circulating HO-1 correlated directly with the mean blood pressure of the patients (66). These studies support a correlation between altered HO-1 and preeclampsia, but do not determine causation. Several studies, however, have looked at the effect of hypoxia on the production of heme oxygenases by placental tissues in vitro. In the first, McCaig and Lyall (40) exposed villous explants from human placentas to an anoxia-reoxygenation injury with exposure to either physiological (5%) or superphysiological (20%) concentrations of oxygen. Surprisingly, in no treatment protocol was any change observed in the expression of either HO-1 or HO-2 (40). In contrast, our laboratory has exposed rodent placental villous explants to chronic (48 h) hypoxia at 1% oxygen, and observed a marked increase in HO-1 compared with explants cultured at physiological (6%) oxygen tensions, as would be expected if HO-1 is acting as a hypoxia-sensitive factor (23). Further work, including the direct role of chronic hypoxia on HO-2 expression in these tissues remains to be determined, as does the molecular signaling events that could be regulating HO-1 expression in these tissues in response to chronic ischemia.

**Heme Oxygenases as Therapeutics in Obstetrical Complications**

Besides the potential role of heme oxygenases in the development of preeclampsia, several groups have suggested that induction of HO or administration of its metabolic byproducts, CO and bilirubin, could be effective therapeutic approaches for the management of the preeclampsia patient and for the prevention of immunologically induced miscarriage (2, 3, 76). This has largely been based on the observed ability of HO-1 to interfere with known pathophysiological pathways that are active in the preeclampsia patient: overproduction of sFlt-1, inflammatory cytokine production, and increased oxidative stress. This has led to a series of studies examining the effects of HO-1 on these pathways in vitro, and more recently, its utility in attenuating the symptoms of preeclampsia in preclinical animal models of preeclampsia and spontaneous miscarriage, both of which are hypothesized to result from defects in placental development.

The overproduction of sFlt-1 is one of the most consistently studied pathogenic mechanisms in preeclampsia research. The loss of bioavailable VEGF is believed to be one of the central mechanisms leading to maternal endothelial dysfunction in these patients, and increased sFlt-1 has repeatedly been shown to cause hypertension in animal models (21, 37). As such, it is an often proposed target for intervention in preeclampsia. An interesting paper from the Ahmed laboratory first connected HO-1 with suppression of sFlt-1. As seen in Fig. 3, Cudmore et al. (14) found that VEGF or interferon-γ-induced sFlt-1 from placental explants could be reduced by induction of HO-1. Furthermore, this effect was attributed to the actions of CO, as administration of CO-releasing molecules mimicked the effect without induction of the protein itself (14). More recently, our laboratory has examined the effects of HO-1 and
We have recently carried out a series of experiments to determine the effects of HO-1 induction on several in vivo models of hypertension, which are associated with preeclampsia. In the first, we utilized the reduced uterine perfusion pressure (RUPP) rodent model, which uses constrictive silver clips to artificially restrict blood flow to the uterus in late gestation, leading to placental ischemia. This model closely mimics the pathophysiological symptoms observed in late-stage preeclampsia, including hypertension, proteinuria, maternal endothelial dysfunction, fetal growth restriction, and reduced renal hemodynamics (35). As seen in Fig. 5A, RUPP treatment induces a ~25 mmHg increase in mean arterial pressure on gestational day 19, an effect which is significantly reduced by CoPP-mediated induction of HO-1. Promisingly, this was associated with both a net proangiogenic shift in the ratio of sFlt-1/VEGF in the maternal circulation (Fig. 5B) and a reduction in placental oxidative stress and NADPH oxidase activity, compared with RUPP animals, although mildly increasing both in control groups for reasons that are not clear (Fig. 5, C and D) (22). Subsequent molecular analysis of cell death and survival pathways in the placentas of RUPP rats found a significant increase in injury-mediated cell death pathway activation compared with healthy controls, specifically JNK/STAT1/caspase 3 activation. Promisingly, CoPP-mediated induction of HO-1 augmented the activation of the pro-survival ERK/STAT3 pathways, suppressed JNK/STAT1/caspase 3 activation, and restored intracellular ATP levels (Fig. 6) (21). Together, this suggests that HO-1 induction can attenuate cellular injury resulting from chronic underperfusion of the placenta and suggests one mechanism by which HO-1 induction can attenuate the symptoms of placental ischemia-induced hypertension.
We have also examined the effect of HO-1 induction on sFlt-1-derived hypertension in pregnant rodents. Infusion of sFlt-1 to levels similar to that seen in response to placental ischemia results in a 17-mmHg increase in blood pressure, an effect that was entirely blocked by HO-1 induction (Fig. 7A). Interestingly, induction of HO-1 had virtually no effect on placental angiogenic balance, and only minor increases in circulating VEGF. There was, however, a significant decrease in the production of maternal vascular endothelin-1 production (Fig. 7B), suggesting a possible direct effect on the maternal vasculature (21). We have also recently completed a study examining the beneficial effects of HO-1 induction on TNF-α-mediated hypertension in the pregnant rat and have observed similar beneficial effects to that seen in both the RUPP and sFlt-1 model (unpublished data).

Taken together, these studies suggest that HO-1 induction could be acting through multiple pathways to attenuate the symptoms of placental ischemia-induced hypertension, a key component to the etiology of preeclampsia. Further, the in vitro evidence suggests that both CO and bilirubin could independently have potential therapeutic value. In the absence of small-molecule inducers of HO-1, therapies such as low-dose CO inhalation could prove useful for the management of these patients. Indeed, intriguing epidemiological evidence supports this hypothesis. Both increased environmental CO exposure and maternal smoking (but not the use of smokeless tobacco) have been associated with decreased rates of preeclampsia in large-scale studies (69, 79). Future studies examining the use of CO in moderating the effects of placental ischemia-induced hypertension should prove interesting.

**Conclusion**

Once considered simply a housekeeping system, the heme oxygenases have emerged as an important player in cardiovascular function and hypertension. More recently, their importance in the establishment and maintenance of a healthy pregnancy has begun to be appreciated. Heme oxygenases are now known to be important for the establishment of placental blood flow and response to hypoxic stress in the placenta. Irregularities in the system may lie at the root of several obstetrical problems. They also hold promise as potential therapeutics for the management of these same disorders, and future research into the utility of the system may finally provide therapeutic options for the management of the preeclampsia patient.

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