Role of the renin-angiotensin system in the pathogenesis of preeclampsia

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Shah, Dinesh M. Role of the renin-angiotensin system in the pathogenesis of preeclampsia. Am J Physiol Renal Physiol 288: F614–F625, 2005; doi:10.1152/ajprenal.00410.2003.—Preeclampsia is a hypertensive disorder unique to pregnancy with consistent involvement of the kidney. The renin-angiotensin system (RAS) has been implicated in the pathogenesis of preeclampsia. In the gravid state, in addition to the RAS in the kidney, there is a tissue-based RAS in the uteroplacental unit. Increased renin expression observed both in human preeclampsia and in a transgenic mouse model with a human preeclampsia-like syndrome supports the concept that activation of the uteroplacental RAS, with angiotensin II entering the systemic circulation, may mediate the pathogenesis of preeclampsia. A novel disease paradigm of the two-kidney one-clip (2K-1C) Goldblatt model is presented for preeclampsia, wherein the gravid uterus is the clipped “kidney” and the two maternal kidneys represent the unclipped kidney. Validation of the 2K-1C Goldblatt model analogy requires evidence of elevated angiotensin II in the peripheral circulation before vascular maladaptation in preeclampsia. Convincing evidence of the elevation of angiotensin II in preeclampsia does not exist despite the fact that much of vascular pathogenesis appears to be due to angiotensin type I (AT1) receptor activation. Vascular maladaptation with increased vasmotor tone, endothelial dysfunction, and increased sensitivity to angiotensin II and norepinephrine in manifest preeclampsia may be explained on the basis of angiotensin II-mediated mechanisms. Recently, novel angiotensin II-related biomolecular mechanisms have been described in preeclampsia. These include AT1 and bradykinin B2 receptor heterodimerization and the production of an autoantibody against AT1. Various organ systems with a predilection for involvement in preeclampsia are each a site of a tissue-based RAS. How angiotensin II-mediated mechanisms may explain the primary clinical-pathological features of preeclampsia is described. Future investigations are proposed to more precisely define the role of activation of the uteroplacental RAS in the mechanisms underlying preeclampsia.

HYPERTENSIVE DISORDERS COMPLICATE approximately 5–7% of all pregnancies (35a). These disorders include 1) chronic hypertension of whatever origin, including essential hypertension and chronic renal disease; 2) gestational hypertension, a hypertensive disorder occurring in pregnancy without multisystem involvement; 3) preeclampsia syndrome superimposed on chronic hypertension; 4) preeclampsia syndrome occurring de novo and only in the first pregnancy; and 5) preeclampsia syndrome occurring in a subsequent pregnancy and/or recurring with an underlying susceptibility state.

Preeclampsia is a unique syndrome of pregnancy characterized by hypertension, proteinuria, and, frequently, edema. Several pathophysiological mechanisms have been implicated in the development of preeclampsia. These include endothelial dysfunction (36), an inflammatory pathway (48), oxidative stress (73), activation of thrombosis (37), and the renin-angiotensin system (RAS) (85). Endothelial dysfunction and oxidative stress have been previously reviewed (59, 99). Deficient uteroplacental perfusion is well recognized to be a feature in all preeclampsia syndromes (91). The RAS may be one of the mechanisms underlying the deficiency of uteroplacental perfusion. Recent investigations of the RAS in preeclampsia have highlighted a need for a comprehensive review of this subject.

The purposes of this paper are to 1) review recent investigations of the role of the RAS in the pathogenesis of preeclampsia and explain the observations on the circulating RAS in preeclampsia; 2) present a two-kidney one-clip (2K-1C) Goldblatt model paradigm for activation of the RAS in preeclampsia; 3) review mechanisms responsible for vascular maladaptation and explain the clinical manifestations of preeclampsia; and 4) propose a concept that the activation of the uteroplacental RAS may be an important biochemical mechanism in the pathogenesis of preeclampsia. Based on these, future investigations have been proposed in this field.

BACKGROUND

Renal Analogy for the Gravid Uterus

To conceptualize the role of the uteroplacental RAS in the pathogenesis of preeclampsia, it is necessary to describe briefly the similitude between the kidney and the gravid uterus. Embryologically, the kidney and the uterus develop in close proximity to each other from metanephroi and paramesonephric ducts, respectively, from the cells of mesodermal and endodermal origin, both of which are of common epiblast cell origin (65, 66). In mature organs, there is a similarity in the
anatomic layout of the vasculature. Both organs have arcuate vessels at the periphery with radially placed branches, the radial arteries, from which or from whose branches arise the spiral and glomerular arteries of the uterus and kidney (15, 28, 88, 97). The spiral arteries of the uterus in the gravid state with placental development are incorporated into the uteroplacental unit and become the decidual vessels, which are the afferent vessels of the maternal intervillous blood flow. The decidual veins serve as the efferent outflow channels. The intervillous flow is much larger than any other capillary bed, and the maternal intervillous flow to the uteroplacental unit in the gravid uterus is the conceptual counterpart of glomerular flow in the kidney. Reviews on the uteroplacental circulation allow one to appreciate this comparison further (20, 97). The biochemical vasomotor mechanisms that regulate blood flow within these two organs are also similar. Both organs produce eicosanoids, endothelin, and nitric oxide (NO) and both organs have an independent RAS.

The Uteroplacental RAS

In the gravid state, the formation of the placenta incorporates maternal uterine tissue, primarily the decidua, with the fetoplacental tissue to form a functional uteroplacental unit. Thus major maternal components of the placenta include the decidua and decidual blood vessels. From the point of view of cellular origin, there are actually two RAS in the placenta, one in the fetal placental tissue and the other in the maternal placental tissue, i.e., the decidua.

All of the components of a RAS exist in the fetal tissues of the placenta. Stakemann (112) originally described a renin-like pressor substance isolated from the cat placenta. Later, Symonds et al. (115) reported renin secretion from chorionic cells in culture. Renin and angiotensinogen gene expression was subsequently confirmed in the human placenta (60). We cloned and sequenced full-length prorenin cDNA from human fetal-placental tissue that is identical to renal prorenin (68). The presence of angiotensin-converting enzyme (ACE) and the angiotensin II type 1 receptor (AT1) in the vasculature has been previously confirmed in the human placenta (60). We cloned renin, ACE, and AT1 expression in the first-trimester decidua using RT-PCR and have localized the expression of these components by in situ hybridization and immunohistochemistry in and around the spiral arteries. We have recently presented molecular evidence for the presence of renin and angiotensinogen expression, with sequences similar to the respective renal and hepatic genes, in prolactin-producing human decidual cells from the third trimester of pregnancy (67).

This molecular evidence of a tissue-based RAS in the decidua may have the following implications. The local spiral artery RAS may play a role in the pregnancy-associated vascular modeling of the spiral arteries (81). The synthesis of renin and angiotensinogen in the prolactin-producing endocrine cells of the decidua has implications for the regulation of this RAS (67). Transformation of uterine-lining endometrial stromal cells to the decidual cells of pregnancy and expression and secretion of prolactin are regulated by estrogen, progesterone, and several other paracrine factors (129). The sex steroids also regulate hepatic angiotensinogen expression (87). Therefore, we have proposed that the decidual RAS may also be regulated by estrogen and progesterone and by other factors involved in decidualization (67). Progesterone treatment of decidual cells or endometrial stromal cells in vitro increases active renin secretion (108, 124), and progesterone increases renin mRNA abundance in stromal decidual cells in vivo (125). Uterine renin secretion is a constitutive secretion, with a response time of hours for various stimuli compared with renal renin, which has a regulated secretion, cells having storage granules and a response time of few minutes (111).

Thus in human pregnancy, on the maternal side, there are two major renin-producing circulations, namely, renal circulation and uteroplacental circulation. Experimentally, in pregnant rabbits, a reciprocal relationship between uterine and renal renin synthesis has been demonstrated; i.e., when uterine renin synthesis is increased, renal renin synthesis is reciprocally decreased (40). A complete local tissue-based RAS in the uteroplacental unit may regulate the regional maternal intervillous blood flow (85).

The Circulating RAS in Normal Pregnancy

Normal pregnancy is characterized by an early increase in the circulating levels of renin (58). The origin of this increase has been ascribed to both ovarian secretion of renin and the decidual production of renin (105, 109). Angiotensinogen levels also increase in pregnancy, but the exact timing of this change is not very well defined. Aldosterone levels are increased, and this may contribute to sodium retention and resultant obligatory water retention, which is one of the mechanisms of volume expansion in pregnancy (21). The effect of ANG II on the systemic vasculature would be expected to increase vasomotor tone; however, pregnancy is characterized by a lack of such a response. The systemic vasculature is thus refractory to ANG II in normal pregnancy, i.e., requires a higher ANG II infusion rate (almost twice as high compared with nongravid at the peak refractory state) for the same degree of vascular response (3, 45). This vascular refractoriness to ANG II in pregnancy has been ascribed, in part, to progesterone and prostacycline (47).

The RAS in Preeclampsia

Observations of the circulating RAS in preeclampsia. Preeclampsia may present with variable manifestations of the multiple systems involved but is most consistently associated
with renal involvement. The RAS has been implicated in the pathogenesis of preeclampsia (85). Many of the previous investigations of the RAS in pregnancy and preeclampsia involved, out of contemporaneous necessity, measurements of the components of the RAS in the peripheral blood or ANG II infusion and support the following observations. First, while renin, angiotensinogen, ANG II, and aldosterone are increased in the peripheral blood in normal pregnancy (110), in patients with preeclampsia, plasma renin activity and aldosterone are paradoxically suppressed with relatively higher levels of aldosterone for the given level of renin (23, 114), suggesting increased adrenal sensitivity to ANG II. Second, normal pregnancy is associated with decreased vascular responsiveness to ANG II (3), and preeclampsia is associated with increased sensitivity to ANG II that may develop before the clinical manifestations of the disease (45).

A decrease in ANG-(1-7), the vasodilatory arm of the RAS in the maternal peripheral plasma, has been reported in preeclampsia (80). All other components of the renin-angiotensin-aldosterone system, except serum ACE, were reduced in preeclamptic subjects compared with normal pregnant subjects. The effect of ANG-(1-7) on uterine blood flow is unknown. Hayashi et al. (54) prospectively investigated the response of endogenous ANG II levels in 55 primigravid patients during the last half of pregnancy. Blood samples were obtained from patients in the lateral and supine recumbent positions. They identified that the mean supine ANG II level was significantly higher between 29 and 34 wk of gestation in patients destined to develop preeclampsia than in those who remained normotensive (54). This difference in the ANG II levels is partially explainable by lower plasma renin activity levels in the controls compared with preeclamptic subjects in this study. In women with chronic hypertension who develop superimposed preeclampsia initially, at 20- and 28-wk gestation, the RAS remains elevated, similar to women who are not destined to develop preeclampsia. In women who develop preeclampsia, plasma renin activity at 32 and 38 wk and aldosterone at 32 wk are lower compared with controls (12). These observations suggest that after the establishment of increased sensitivity to ANG II, renal renin and adrenal aldosterone secretions are apparently suppressed. The renal renin juxtaglomerular cell granularity in manifest preeclampsia is decreased (57), which is consistent with the decrease in renal renin secretion. Maternal circulating renin in human pregnancy represents renal renin because it responds appropriately to renal-type physiological stimuli (22). The decrease in renal renin secretion may thus explain why the maternal circulating level of renin is decreased in women with manifest preeclampsia. However, currently there is no convincing evidence that circulating renin or ANG II is increased in preeclampsia in the pathogenesis phase.

Renin gene overexpression studies. Endocrine characteristics of preeclampsia include increased vascular and adrenal ANG II sensitivity and low systemic renin levels. Nonpregnant transgenic animal models with regional overexpression of the renin gene have similar endocrine features (13). These animals respond to ACE inhibitors with a decrease in blood pressure, which implies that regional activation of the RAS contributes to their hypertension (14). By analogy to these animal models of renin overexpression, we hypothesized that renin gene expression in uteroplacental tissues is increased in preeclampsia. The level of renin gene expression in the parietal decidua (decidua vera) was threefold that in the control in preeclampsia, but it is similar in the basal decidua and chorionic villous fetal-placental (nonvascular) tissue (107).

The regional increase in decidual renin gene expression and its protein products prorenin-renin with local and circulating angiotensinogen may result in a modest increase in ANG II production on the maternal side. Initially, modestly increased ANG II may help increase the maternal intervillous/uterine blood flow similar to that demonstrated experimentally in pregnant dogs, sheep, and rabbits by bolus or continuous infusion of ANG II (11, 41). In the former study, angiotensin infusion resulted in increased arterial pressure and a reduction in renal flow but an increase in femoral, uterine, and carotid artery flow as measured by arterial flow probes. Cardiac output was measured by the Fick method and did not change after ANG II infusion. The mechanism by which this increase may occur has not been elucidated but may be related to an increase in systemic pressure and a decrease in vascular resistance as suggested by the authors (11). Furthermore, epinephrine and norepinephrine infusions in dogs caused blood pressure to rise to the same degree but evoked a marked fall in uterine blood flow despite a rise in iliac flow (11). Other experimental evidence suggests that ANG II does not directly vasoconstrict the uterine vascular bed but that continuous ANG II infusion may increase uterine vascular resistance possibly through a sympathoadrenal mechanism without reducing uterine blood flow (34). If the increase in intervillous blood flow is not sufficient for fetoplacental needs or does not occur, a continued activation of the RAS may result in a state analogous to chronic subpressor dose ANG II infusion. However, well-designed studies have not been conducted to demonstrate such a state in human pregnancy before the development of preeclampsia. A chronic subpressor dose ANG II state may result in systemic vascular modification similar to that seen in chronic experimental subpressor dose ANG II infusion and hypertension in the nongravid state, although this has not been experimentally demonstrated in the gravid state. In women with essential hypertension who develop superimposed preeclampsia, an increase in the uteroplacental blood flow, as measured by the metabolic clearance of dehydroisoandrosterone sulfate, has been shown to occur, followed by a subsequent decline (46).

EXPERIMENTAL ANIMAL MODELS: PREECLAMPSIA AND THE RAS

Elevated renin secretion in the maternal uteroplacental circulation has been demonstrated in an experimental primate model of preeclampsia produced by chronic reduction of uterine blood flow; however, the study was limited by including one pregnant control and three nonpregnant control animals (5). Acute reduction of uterine blood flow in nephrectomized rabbits has been shown to result in a significant increase in uterine and systemic renin levels (41). In pregnant dogs, however, an acute reduction in uterine perfusion pressure by acute aortic constriction accompanied by an elevation in systemic blood pressure did not result in any change in circulating renin levels measured after servo-controlling pressure for 1 h (121). A single renin measurement obtained after servo-controlling pressure may not reflect dynamic reciprocal changes in renal renin secretion that may have occurred during the stabilization. In this experimental model, infusion of captopril, an
ACE inhibitor, together with ANG II, on subsequent acute aortic constriction resulted in a similar systemic blood pressure elevation. This led the authors to conclude that renin may not play a role in the elevation of systemic blood pressure in uterine ischemia (121). These latter experiments can also be interpreted to imply that ANG II infusion mediated the increase in blood pressure, whereas the ACE inhibitor suppressed both renal and uterine RAS activity. The ACE inhibitor was shown to reduce systemic blood pressure to a similar degree in the reduced uterine perfusion pressure rat model as in the control group (7). Although these studies make important contributions in their own right as specific experimental observations, these studies do not answer the question of whether the uterine RAS may be involved in the pathophysiology of preeclampsia. Studies of an acute reduction in uterine blood flow do not represent a correct experimental model by which to investigate this question because preeclampsia is associated with a chronic reduction in uterine blood flow. Global suppression of the RAS with captopril will also suppress the renal RAS and can have a systemic vascular effect in addition to suppressing the uterine RAS. The difference in placentation in nonprimates from placentation in human gestation may be too great for such animal models to be acceptable for the study of preeclampsia pathophysiology. A species in which the uterine decidual RAS has not been defined may not represent the best experimental models by which to investigate this question. An AT₁ antagonist should have been used rather than captopril to investigate the role of ANG II, although many other experimental details about the dose, route of administration, and time of administration will have to be addressed to conduct these experiments appropriately.

Recently, Takimoto et al. (117) reported development of a preeclampsia-like syndrome in an animal model by mating transgenic mice expressing components of the human RAS. Female transgenic mice carrying human angiotensinogen who were normotensive in the nonpregnant state developed hypertension late in gestation when mated with transgenic males overexpressing the human renin gene (117). No other cross-breeds developed the maternal hypertension syndrome during pregnancy. The blood pressure of the pregnant transgenic females began to increase on the day 14 of gestation, continued to rise until the day before delivery (day 20), and returned to the nonpregnant level 3 days after delivery. Concentrations of plasma human renin increased in the maternal circulation, and renin mRNA in the murine placenta gradually increased during gestation, establishing the placental origin of the human renin measured in the maternal circulation. The ANG II levels in the transgenic hypertensive females were fivefold of that observed in normotensive control animals. Although the prorenin and active renin levels in the transgenic females were comparable to those observed in human preeclampsia, ANG II levels are higher in this animal model compared with human preeclampsia. The control wild-type females mated with renin-overexpressing males also showed an increase in renin levels but had normal ANG II levels, and these females did not develop hypertension. Wild-type females mated with wild-type males neither had human renin detected in the maternal circulation nor developed hypertension. This would suggest that excess ANG II mediated the development of hypertension. Treatment of the transgenic hypertensive pregnant females with ES-8891, an inhibitor specific for renin, significantly reduced blood pressure, supporting the role of renin in the pathogenesis of hypertension in this model. The glomeruli were uniformly enlarged, and there was associated proteinuria. However, whether there was glomerular endotheliosis, i.e., swelling of glomerular endothelial cells, regarded as a classic finding in human preeclampsia, is difficult to determine from the published figures. This is a limitation of the images presented, and further investigations are needed to examine the occurrence of glomerular endotheliosis in this model. There was 63% mortality, generalized convulsions occurred in 15% of the animals, and the placenta showed necrosis and edema in the transgenic hypertensive females (117). The action of ANG II in this mouse model appears to be mediated via the AT₁a receptor because hypertension and other effects were not seen in the mother, despite elevated human renin and ANG II levels in the circulation, if the AT₁a gene had been deleted (102).

One of the most remarkable aspects of this transgenic mouse model is its similarity to the clinical features of human preeclampsia, including generalized convulsions and some of the renal findings (117). This transgenic model of hypertension in pregnancy provides experimental evidence to support the concept that renin derived from the uteroplacental circulation and ANG II generated in the maternal circulation may mediate the pathophysiologically of pregnancy-specific preeclampsia-like hypertensive disorders. The amount of human renin from the fetal side that enters the maternal circulation in this mouse model is small relative to the total production of renin in the placenta, and only ~5% of it is in the active form (117). Thus the amount of active renin does not need to be large for it to mediate the pathogenesis of hypertension in the gravid state. In the transgenic model, the fetal placental human renin must enter the maternal circulation to register its effect because it cannot cleave mouse angiotensinogen, but only the human angiotensinogen present on the maternal side (117). Therefore, the pathophysiological events, although dependent on renin expressed in the fetal placenta, occur on the maternal side.

GOLDBLATT MODEL ANALOGY

Human preeclampsia with deficient perfusion in the uterus is a state analogous to the 2K-1C Goldblatt model, with the uterus being the “clipped kidney” and the two maternal kidneys being the “nonclipped kidney” (Fig. 1). In the 2K-1C Goldblatt model, renal renin gene expression in the clipped kidney is increased, whereas it is decreased in the contralateral kidney (103). Reducing uterine perfusion pressure by placement of constrictors and clips, which is analogous to the renal artery clip placement in the Goldblatt model, has been used to develop animal models of hypertension and preeclampsia-like syndrome in several species (6, 8, 29, 33).

In the Goldblatt one-kidney model, the early rise in arterial pressure is caused by the renin-angiotensin mechanism; however, the secretion of renin that rises to a peak in a few hours is normal within 5–7 days (51). In the second phase of one-kidney Goldblatt hypertension, although thought to be volume dependent, there is no evidence that either blood volume or cardiac output is significantly elevated in established hypertension (51); however, peripheral vascular resistance is increased. Although a regional increase in renin expression occurs in uteroplacental tissue in preeclampsia, handling of renal sodium and water is altered in preeclampsia and contrib-
utes to maintaining the hypertension as in renal RAS-mediated hypertension (50). Thus, in preeclampsia, the uteroplacental tissue is simply the surrogate site for activation of the RAS that mediates renal participation in preeclamptic hypertension.

Our data showing increased renin gene expression in human preeclampsia are correspondent with the transgenic mouse model of preeclampsia and to the 2K-1C Goldblatt model (103, 107, 117). The degree of increase in renin gene expression is much higher in this model than in the human syndrome, and it is uncertain whether such an animal model may be developed with only a modest increase in renin gene expression. In the mouse model, the increase in renin expression is in the fetal placental tissue as opposed to the maternal placental tissue, i.e., the decidua in human preeclampsia. Renal renin juxtaglomerular cell granularity in manifest preeclampsia is decreased (57), which is consistent with the 2K-1C Goldblatt model analogy for preeclampsia. We are proposing that, after activation of the decidual RAS, a modest increase in ANG II entering the systemic circulation results in the vascular maladaptation seen in preeclampsia. Under this proposal, renal renin contributes most of the circulating renin; however, because of the reciprocal relationship between uterine and renal renin, as a systemic and organ-specific effect of ANG II is being established, renal renin will be secondarily suppressed but remain responsive to renal-type physiological stimuli.

Our hypothesis, based on the renal analogy, is that chronic reduction in intervillous blood flow may regulate the decidual RAS. In the transgenic model of preeclampsia, renin overexpression is “self-driven,” and in the Goldblatt model the increase in renin expression occurs locally in the clipped kidney, with reduced perfusion pressure and a chronic reduction in renal perfusion. In human preeclampsia, one question that needs to be addressed is by what mechanism the activation of the decidual RAS is mediated. Given the evidence that progesterone regulates the RAS and that progesterone levels are increased in women developing preeclampsia (126), we suggest that placental progesterone may be at least one of the factors to signal the maternal side to activate the decidual RAS.

The most critical evidence necessary for the 2K-1C Goldblatt model analogy of preeclampsia to be validated is the elevation of circulating ANG II before development of the vascular modification seen in human preeclampsia. Such evidence does not exist because well-designed human studies have not been conducted to demonstrate elevated ANG II in preeclampsia. This is despite the fact that much of the vascular pathogenesis is consistent with activation of the AT1 receptor.

**PATHOPHYSIOLOGY OF VASCULAR MALADAPTATION IN PREECLAMPSIA**

The systemic vasculature in preeclampsia is modified functionally, termed here as vascular maladaptation (Fig. 2A). The functional changes in the vasculature in preeclampsia include an increase in peripheral vascular resistance and increased sensitivity to ANG II and norepinephrine (30). In the systemic vasculature, although refractory to ANG II in normal preg-

![Diagram](http://ajprenal.physiology.org/)

The figure is based on data from experimental subpressor angiotensin II infusion hypertension and observations in human preeclampsia. PGI2, prostacyclin; THXA2, thromboxane A2; HETE, monohydroxy fatty acids; ET, endothelin; NO, nitric oxide; AT1, angiotensin receptor type 1; AT1-AA, AT1 autoantibody; AII, angiotensin II; AB, bradykinin receptor; AT2-A2, AT2 autoantibody. B: angiotensin II-dependent oxidative stress, deficient NO-dependent vascular relaxation, and prothrombotic effects in preeclampsia based on experimental subpressor angiotensin II hypertension and observations in preeclampsia. ecSOD, extracellular superoxide dismutase; NF-kB, nuclear factor κB; I-NFKB, inhibitor of NF-κB.
nancy, vascular sensitivity to ANG II increases in preeclamp-
sia. Increased renin secretion from the uteroplacental circula-
tion with increased ANG II, it is hypothesized, may have
effects similar to chronic suppres sor ANG II infusion in the
experimental setting. The underlying mechanisms of the vas-
cular maladaptation in suppres sor ANG II-induced hyperten-
sion can be broadly categorized as 1) functional changes in the
vasculature and 2) structural changes in the vasculature. The
vascular maladaptation of preeclampsia is a reversible func-
tional change, and its mechanism is reviewed here. The struc-
tural change is discussed in the context of the decidual vascular
lesions of preeclampsia.

Circulating Parameters in Vascular Maladaptation

Biochemical evidence for vascular maladaptation has been
investigated extensively using chronic suppres sor ANG II
infusion experimental animal models in the nongravid state.
The early biological effects of ANG II infusion include aldo-
sterone production and increased sodium and volume retention.
Increased sympathetic activity participates in the early and
later phases of hypertension through systemic ANG II effects
and by actions on the central nervous system (72, 98). Other
biochemical evidence of functional changes in the vasculature
include the following aspects: 1) alterations in the cyclooxygen-
ase pathway of arachidonic acid metabolism and increased
thromboxane production (72, 122); 2) alterations in the li-
poxygenase pathway and increased monohydroxy fatty acid
productions (10); 3) PKC-mediated mechanisms and their
effect on calcium handling (119); 4) alterations in Na+/K+
pump mechanisms (89); and 5) a change in endothelin expres-
sion and release (31).

Some of these mechanisms have been investigated in human
preeclampsia. Preeclampsia has been shown to be associated
with an increase in sympathetic activity (104). Thromboxane
A2 synthesis, as measured by urinary excretion of thromboxane
B2 metabolites, has been demonstrated to be significantly
higher in patients with pregnancy-induced hypertension (42).
It has been suggested that the ratio of prostacyclin to thrombox-
ane A2 may be higher in preeclampsia, whereas the absolute
concentrations may not be different (44). The retention of
sodium and water is well recognized to occur in preeclampsia,
and mineralocorticoids have been implicated (70). Sodium
pump activity may be altered in preeclampsia as evidenced by
reduced α2-isoform mRNA levels in myometrial smooth mus-
cle tissue and by the presence of circulating inhibitors of the
sodium pump (71, 74).

Molecular Basis for Vascular Changes

AT1-B2 heterodimerization. Recently, increased heterodimer-
ization of AT1 and the bradykinin B2 receptor has been impli-
cated in increased responsiveness to ANG II in preeclampsia
(2). In platelets and in omental vessels, although AT1 was not
increased, B2 levels were increased four- to fivefold in pre-
eclampsia, and AT1-B2 heterodimerization on platelets corre-
lated with increased B2 protein levels. AT1-B2 receptor het-
erodimerization in the omental vessels in preeclampsia corre-
lated with increased AT1-stimulated G protein activation. B2-
specific antagonists did not suppress ANG II-stimulated G
protein activation in the omental vessels in preeclampsia, sug-
possing ANG II as the agonist for the signal transduction
through the heterodimerized receptors (2). Their data also
suggest that the intracellular domain of the B2 receptor is
involved in ANG II-stimulated signaling. Collectively, these
data support the concept that increased B2 receptor with
AT1-B2 heterodimerization mediates at least part of the in-
creased responsiveness to ANG II in preeclampsia, bypassing
the ANG II refractoriness by using the B2 intracellular domain
for signal transduction (2). AT1 homodimer’s susceptibility to
inactivation by peroxide treatment suggested a role for the
oxidative stress of normal pregnancy to confer some of the
ANG II refractoriness and resistance of AT1-B2 heterodimers
to peroxide inactivation may contribute to enhanced ANG II
responsiveness in preeclampsia (2). Exposure of vascular
smooth muscle cells to ANG II did not increase B2 receptor
protein levels, and the mechanism for increased B2 receptor
remains unclear (2).

Role of AT2 receptors. The ANG II type 2 receptor (AT2)
appears to function as an “antagonist” of AT1 (1). Pregnancy is
associated with an increase in AT2 expression in the uterus
but not in the systemic vasculature in sheep (17). Increased respon-
siveness to ANG II has been demonstrated in the uterine
vasculature during AT2 receptor blockade (79). Enhanced
ANG II reactivity has been observed in the uterine vasculature
with decreased expression of AT2 in sheep exhibiting pre-
eclampsia-like syndrome after ANG II infusion (78). Whether
a similar change in AT2 expression occurs in human pre-
eclampsia is unknown.

Immunological Basis for Vascular Changes

Patients with preeclampsia have been shown to develop an
autoantibody against the AT1 receptor (AT1-AA) (120). The
presence of this autoantibody was demonstrated by the
chrorotopic response, i.e., increased heartbeat rate, to AT1-med-
iated stimulation of cultured neonatal rat cardiomyocytes as
confirmed by effective partial blockade by an AT1-specific
antagonist. Prazosin, an adrenoreceptor antagonist, abolished
the residual antibody-generated response, suggesting a role for
the α1-adrenoreceptor in mediating part of this response. The
cardiomyocyte response to the antibody was blocked by a
peptide corresponding to the sequence of the second extracel-
ular loop of AT1, confirming that the antibody is directed
against this site of AT1. The mechanism by which this antibody
activates signal transduction through α1-adrenoreceptors re-
mains unexplained. These antibodies have been suggested to
facilitate interaction of ANG II with its receptor, which may
play a role in enhancing vascular sensitivity to ANG II. These
data on AT1-AA correlate with the finding of anti-ssDNA and
dsDNA autoantibodies in preeclampsia (123), suggesting an
abnormal or unrestrained B cell activation or perhaps aber-
rantly increased antigen presentation, or both. Collectively,
these data provide evidence that in preeclampsia an autoanti-
tibody against the AT1 may play a role in mediating ANG II
responsiveness through AT1 and α1-adrenoreceptors.

Role of Soluble VEGF Receptor Variant

Soluble fms-like tyrosine kinase 1 (sFlt1), a splice variant of
VEGF receptor Flt1, acts as a potent VEGF and placental
growth factor (PIGF) antagonist (32, 55, 75). Placental expres-
sion of sFlt1 is increased in preeclampsia (128). Increased
circulating sFlt1 in preeclampsia is associated
with decreased circulating levels of VEGF and PI GF, resulting in endothelial dysfunction in vivo that can be rescued by exogenous VEGF and PI GF (75). VEGF and PI GF cause microvascular relaxation of rat renal arterioles in vitro that is blocked by sFlt1, although sFlt1 alone did not cause significant vasoconstriction (75). Administration of adenovirus overexpressing murine sFlt1 to pregnant rats induced hypertension, proteinuria, and glomerular endotheliosis (75). These observations suggest that excess circulating sFlt1 may contribute to the pathogenesis of preeclampsia. The mechanism for excessive placental production of sFlt1 in preeclampsia has not been defined.

In summary, new insight into enhanced ANG II responsiveness in preeclampsia is found in mechanisms involving AT1-B2 heterodimerization and/or AT1-AA. These mechanisms result in enhanced AT1-, adrenoreceptor-, and B2-mediated vascular reactivity, increased vascular resistance, and other ANG II-mediated effects. Endothelial dysfunction, hypertension, and proteinuria may also result from decreased availability of NO and excess sFlt1.

PROPOSED CONCEPT TO EXPLAIN ROLE OF ANG II IN PRIMARY PATHOGENIC FEATURES OF PREECLAMPSIA

An increase in effective ANG II and α1-adrenoreceptor signal transduction will result in AT1-mediated and adrenoreceptor-mediated cellular events, which, along with increased sFlt1, may help explain the primary pathogenic features of preeclampsia, including 1) increased vasomotor tone with the development of hypertension and vascular-endothelial dysfunction, 2) involvement of kidney and other organs with the local RAS, 3) decidual vascular lesions of preeclampsia, and 4) activation of the thrombosis pathway.

Vasomotor Events and Vascular-Endothelial Dysfunction

ANG II, acting through AT1 receptor activation of vascular smooth muscle cells, increases vasomotor tone, which is then maintained through several mechanisms mediated by ANG II. This results in increased peripheral vascular resistance and hypertension, which are key features of preeclampsia.

The role of sympathetic system activation has been well recognized in ANG II-mediated hypertension (72, 98). The postganglionic sympathetic nerve activity in skeletal muscle blood vessels is more than three times as high in preeclamptic as in normotensive pregnant women (104). Stimulation of sympathetic neurons with plasma from eclamptic and preeclamptic women significantly increases norepinephrine release, but whether this is mediated through ANG II has not been defined (63). ANG II-mediated experimental hypertension in the nonpregnant state is associated with a marked increase in vascular smooth muscle immunostaining for endothelin, and blockade of the endothelin receptor ETA corrects the vasoconstrictor hyperresponsiveness (96). Suppressor dose chronic ANG II infusion increases blood pressure, accompanied by an increase in oxidant stress, which is prevented by endothelin receptor blockade (90). Whether systemic levels of endothelin are increased in preeclampsia is controversial (86, 118), but endothelin may mediate the vascular response locally in preeclampsia without a change in the circulating levels (106).

Oxidative stress has been implicated in the vascular dysfunction of preeclampsia (59) (Fig. 2B). Reactive oxygen species superoxide anion (O2-) has been implicated in ANG II-mediated hypertension (76). ANG II generates O2- in the vascular smooth muscle cells through stimulation of NADPH (reduced form of nicotinamide adenine dinucleotide, i.e., NADH) and NADPH (reduced form of nicotinamide adenine dinucleotide phosphate, i.e., NADP) oxidase activity (49). ANG II generates reactive oxygen species in mitochondria through stimulation of an inhibitor of NF-κB degradation and by activation of nuclear factor-kB in the endothelial cells (94). ANG II also increases extracellular superoxide dismutase (ec-SOD) mRNA levels in vascular tissues (43). This ecSOD is the major form of SOD in the vascular tissue. Increased ecSOD is not a result of hypertension per se, because a similar level of hypertension induced by norepinephrine had no effect of ecSOD expression. Instead, it is a specific action of AT1 activation (43). These experimental data in the non gravid state support the concept that ANG II-mediated hypertension in pregnancy also may be due, in part, to effects on the oxidative state in vascular-endothelial tissue. ANG II-mediated oxidative stress is associated with impaired relaxation to acetylcholine, the calcium ionophore A-23187, and nitroglycerin, suggesting a role for NO in the ANG II effect on vasomotor tone (95). In preeclampsia, there is impaired endothelium-dependent relaxation in the omental resistance arteries (92). NO is also known to react with superoxide anions produced under conditions of oxidative stress, yielding peroxynitrite, which may also impair vascular function. There is increased endothelial NO synthase, decreased SOD, and increased nitrotyrosine in maternal subcutaneous vessels in preeclampsia (100). This suggests that increased oxidative stress, peroxynitrite formation, and hence decreased NO bioavailability may contribute to the impaired vasorelaxation in preeclampsia. In view of the experimental evidence that ANG II causes oxidative stress, despite increased NO production, given that oxidative stress may lead to peroxynitrite formation, we suggest that these aberrations of vascular and endothelial function and resultant impairment of vasorelaxation may be induced by ANG II in the pathogenesis phase and maintained through the sustained AT1 activation.

Given that in manifest preeclampsia increased vasomotor tone may be maintained through several mechanisms, it should not come as a surprise that an ACE inhibitor only partially reduced hypertension in postpartum preeclampsia (113). Such experimental interventions performed when the uteroplacental RAS is undergoing dynamic changes at delivery with the removal of the placenta decidua make these data difficult to interpret.

Involvement of the Kidney and Other Organs with Local RAS

Organs expressing components of the RAS appear to be more frequently compromised in preeclampsia (Fig. 3). On vascular maladaptation and increase in vascular sensitivity to ANG II and norepinephrine, with decreased NO bioavailability and with excess sFlt1, renal vasconstriction may progressively occur, resulting in deterioration of renal function.

Endothelial dysfunction in the kidney in preeclampsia is demonstrated by proteinuria and by morphological evidence of glomerular endotheliosis. Recently, excess circulating placen-
Angiotensin II-mediated decidual vascular lesions and multiorgan involvement of kidneys, liver, and brain in preeclampsia. Note that all sites involved have a tissue-based RAS. ROS, reactive oxygen species; MCP-1, monocyte chemoattractant protein-1; GFR, glomerular filtration rate; sFlt 1, soluble fms-like tyrosine kinase 1; CVA, cerebrovascular accidents.

Women with preeclampsia have reduced plasma renin and aldosterone but relatively greater stimulation of aldosterone than normal pregnant women, which suggests enhanced sensitivity of the adrenal gland to ANG II (23). This relative, functionally excess aldosterone responsiveness may contribute to sodium and water retention. Whether the renal tubular response to exogenous aldosterone is enhanced in preeclampsia has not been investigated. However, women with preeclampsia, on infusion of saline, retain sodium avidly; i.e., they retain sodium similar to salt-depleted normotensive women without stimulation of plasma renin activity or plasma aldosterone concentration (21). This suggests enhanced renal responsiveness to endogenous mineralocorticoids in preeclampsia. Another potential mechanism postulated in decreased renal glomerular perfusion and increased reabsorption of sodium by distal tubules is reduced kallikrein synthesis, resulting in predisposition to an elevation of blood pressure (93).

Preeclampsia is generally associated with mild cholestasis. ANG II-mediated mitochondrial dysfunction secondary to oxidative stress may contribute to mild cholestasis seen in preeclampsia. In the liver, hepatic vascular dysfunction in preeclampsia is explained by the hepatic vasculature’s responsiveness to ANG II, which has been exploited to reduce blood flow to normal hepatic tissue to direct chemotherapeutic agents more selectively to hepatic cancer metastasis (62). Thus vascular actions of ANG II and mitochondrial injury may contribute to the mild cholestasis of preeclampsia and to cellular injury-mediated release of hepatic enzymes.

The brain has its own RAS, and both the central vasculature and other central nervous system cells are responsive to ANG II, mediating increased sympathoadrenal mechanisms (35, 61). An angiotensinergic neural pathway from parvocellular neurons of the hypothalamic paraventricular nucleus may drive premotor neurons in the rostral ventrolateral medulla to increase central sympathetic activity and arterial blood pressure (77). McKinley et al. (77) and other reviews contain details on RAS-mediated sympathetic mechanisms. Hyper- and hypoperfusion in cerebral blood flow, as suggested in preeclampsia (16), may result from actions of ANG II (116). Vascular dysfunction and endothelial cell injury in the central vasculature may result in neuronal cellular injury and cerebral edema and explain the development of grand mal seizures, i.e., eclampsia, and, occasionally, even with coma.

Decidual Vascular Lesions of Preeclampsia

Hertig (56) described vascular lesions in the uteroplacental vessels characterized by prominent lipid-rich foam cells. Zeek and Assali (127) termed these lesions acute atherosis. DeWolf and associates (38) have described the evolution of these vascular lesions as endothelial damage, deposition of plasma proteins into the vessel walls, and proliferation of myointimal cells, followed by lipid accumulation in myointimal cells and in macrophages recruited to the vessel wall. In women with preexisting hypertension, these lesions are associated with hypertension of the vascular wall. ANG II induces monocyte migration through an AT1-dependent process (64). Monocyte chemoattractant protein-1 (MCP-1) is upregulated in the vascular wall of animals made hypertensive with ANG II or norepinephrine (26). ANG II-mediated induction of MCP-1 and the resultant macrophage recruitment may contribute to vascular hypertrophy (25). The macrophage recruitment in the vascular lesions of preeclampsia may be an action of ANG II, and vascular hypertrophy may, in part, be a consequence of the macrophage infiltration in the vascular wall.

Procoagulant and Prothrombotic Effects

Activation of coagulation and prothrombotic events is a well-recognized phenomenon in preeclampsia (Fig. 2B). Tissue factor (TF) binds to factor VII and active factor VII to form a complex for coagulation, leading to fibrin formation (84). ACE inhibitors reduce TF expression in activated monocytes (83). Autoantibody to AT1 implicated in the TF expression in the placenta and endothelial cells on the maternal side may further contribute to this pathway (39). ANG II through AT1 increases thrombin receptor gene expression in the vascular smooth muscle via a redox-sensitive mechanism (27). ANG II has several other prothrombotic effects that involve platelet activation, plasminogen activator inhibitor type 1, tissue plasminogen activator, tumor necrosis factor, and interleukin-1 (24, 83). Platelet activation and prothrombotic events in preeclampsia can thus be explained to be secondary to ANG II. Platelet activation is well recognized to occur in essential hypertension and is an important contributor of hypertension related comorbidities (18). Although the RAS is acknowledged in this platelet activation, several different classes of antihypertensive agents have shown a salutary effect on the platelet dysfunction in essential hypertension (18). Thus other mechanisms may be involved in platelet dysfunction in preeclampsia.
PROPOSED FUTURE INVESTIGATIONS

According to the Goldblatt paradigm as applied to the uterus, there should be evidence for increased uterine renin secretion, which may transiently increase circulating renin in preeclampsia. What the subsequent changes would be in the circulating RAS parameters will depend on the reciprocal interactions between the uterine and the renal RAS. However, for the 2K-IC analogy to be valid, ANG II should increase at least transiently in the circulation before development of preeclampsia. Inadequate longitudinal studies have been conducted to examine this and other aspects of RAS biology in preeclampsia. To critically examine the proposed role of the uteroplacental RAS, it would be necessary to investigate these concepts using experimental animal models and to develop additional corroborative evidence in human preeclampsia. One line of investigation should be to examine the changes in the peripheral blood RAS parameters chronologically, using animal models of preeclampsia created by reduction in uterine perfusion pressure by techniques similar to those used for Goldblatt models (5, 6, 8, 29, 33). Our hypothesis that a chronic reduction in intervillous blood flow may regulate the decidual RAS is worthy of experimental investigation. These experiments should also aim to validate the reciprocal relationship between the renal and the uterine decidual RAS (5, 40). Corroborative human studies should include verification of changes in the peripheral blood RAS parameters and their chronology. Specifically, there is a need to establish more convincing evidence of increased ANG II in the pathogenesis phase of human preeclampsia, through well-designed longitudinal studies of human pregnancies. Another line of investigation should be to delineate the biomolecular events secondary to uteroplacental renin overexpression in animal models to validate the role of the RAS in the pathogenic pathway (117). These investigations should include study of the biomolecular mechanisms of the vascular dysfunction observed in preeclampsia (2, 39, 120). Furthermore, an ANG II-mediated hypertension model in pregnancy needs to be established by subpressor dose ANG II infusion in the gravid state for elucidation of mechanistic data on the pathogenesis of preeclampsia. A functional genomics approach may help to better define the pathways of the biological network involved in the pathophysiology of preeclampsia. An investigation of the genomics should account for the evidence that there is a familial susceptibility to develop preeclampsia. To determine which biochemical events occur early and which changes may be secondary, it would be necessary to investigate not only the chronology of most significant biochemical changes but also to apply creative approaches to a biological network analysis to define the hierarchy of the biochemical pathways (9, 19).

CONCLUSION

In summary, preeclampsia may not have a single cause but involves multiple pathophysiological pathways. Vascular-endothelial dysfunction, oxidative stress, and autoimmunity may be important mechanisms. This comprehensive review provides evidence that there is a need for further research to examine whether the activation of the decidual uteroplacental RAS may be an important biochemical mechanism in the pathogenesis of preeclampsia.

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REFERENCES


