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Sympathetic nervous system control of vascular function and blood pressure during pregnancy and preeclampsia

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Abstract

Proper vascular tone and blood pressure regulation during pregnancy are important for immediate and long-term cardiovascular health of the mother and her offspring. Preeclampsia (PE) is clinically defined as new-onset maternal hypertension accompanied by cardiovascular, renal and/or neural abnormalities presenting in the second half of pregnancy. There is strong evidence to support that PE is mediated by attenuations in uteroplacental vascular remodeling and increases in vasoconstriction with subsequent placental ischemia/reperfusion-induced release of hypertensive substances into the maternal circulation. These include anti-angiogenic and pro-inflammatory factors. There is also evidence implicating increased sympathetic nervous system activity (SNA) in this maternal disorder, but this mostly includes data correlating severity of disease with catecholamine levels and elevated muscle SNA. These measurements have not confirmed a causative role for SNA in the pathogenesis of PE. Therefore, studies are needed to provide a comprehensive understanding of SNA and its control of vascular function and blood pressure regulation during normal pregnancy in order to set the stage for exploring the mechanisms mediating the exaggerated SNA and signaling during PE. This review examines the role of SNA in control of uteroplacental vascular tone and blood pressure regulation during normal pregnancy. Furthermore, it is proposed that over-activation of the SNA contributes to altered uteroplacental vascular tone and perfusion leading to placental ischemic events and modulates the systemic vasoconstriction and hypertensive responses to soluble placenta ischemic factors. Recognizing the integrative role and importance of SNA in the pathophysiology of PE will advance our understanding of this maternal disorder.

Keywords

autonomic nervous system; hypertension; placental ischemia; vasoconstriction; women's health

Introduction

Preeclampsia (PE) is a complex maternal disorder, which is defined clinically by new-onset hypertension with a maternal blood pressure of $\geq 140/90$ mmHg accompanied by proteinuria in the second half of pregnancy. If proteinuria is not present, the diagnosis can be made with

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the occurrence of hypertension plus pulmonary edema, oliguria, persistent headaches, epigastric pain and/or impaired liver function, thrombocytopenia, oligohydramnios, decreased fetal growth, or placental abruption [1]. As the most effective ‘cure’ for PE is early delivery of the placenta, PE is thought to originate from placental dysfunction [2]. Reduced vascular adaptations in the uteroplacental unit and placental ischemia/reperfusion and hypoxia [3, 4] elicit the release of pro-hypertensive factors into the maternal circulation, which include anti-angiogenic factors and pro-inflammatory factors [5, 6]. Collectively, this milieu targets the maternal vasculature leading to endothelial dysfunction and reduced vasoconstriction-buffering mechanisms in the blood vessel wall supporting the development of hypertension [7]. Thus, it is hypothesized that PE can occur via a two-stage process: 1) the development of reduced perfusion in the uteroplacental circulation and 2) placental ischemia/hypoxia-induced release of soluble placental factors that promote maternal endothelial dysfunction, vasoconstriction, and hypertension in PE.

While evidence supports that placental ischemia and subsequent vascular dysfunction promote the hypertension in PE [8–15], less is known about the role that the sympathetic division of the autonomic nervous system plays in the two-stage theory mediating the pathogenesis of this maternal disorder. Associational studies have found that sympathetic nervous system activity (SNA) is exaggerated before the onset of, and during, maternal hypertension in PE. However, a causative role for this system in the development of placental ischemia or promoting and maintaining the hypertension in PE is only now beginning to be examined. The goal of this review is to discuss the studies in humans and experimental animal models demonstrating that SNA and adrenergic receptor-induced vasoconstriction is elevated in PE. Although there are repeated data to support that these pathways are elevated in PE, the mechanisms mediating this elevation and intervention studies determining whether it contributes in any part of the two-stage process of placental ischemia-induced hypertension is not fully realized. It is proposed that early elevations in SNA encourage placental ischemia/reperfusion events and hypoxia-induced release of pro-hypertensive factors into the maternal circulation. It is also possible that placental ischemic factors reduce the ability of the vasculature to buffer vasoconstriction in response to the elevated SNA in PE. Moreover, it is hypothesized that soluble placental ischemic factors also target the brain to stimulate and maintain increases in SNA. Therefore, the overall impact of these integrative pathways would be to encourage SNA and signaling of this system in the vasculature. Overall, this would result in greater sympathetic tone and hypertension during PE. In order to set the stage for this discussion of mechanisms and cardiovascular outcomes of elevated SNA in PE, this review begins with a colloquy of baseline information about SNA during normal pregnancy.

SNA during normal pregnancy

During normal pregnancy, SNA is actually increased [16]. It is thought that this is a compensatory response to prevent the increasing vasodilation and plasma volume expansion (PVE) in normal pregnancy from going completely unchallenged [17–19]. This thought stems from observations that SNA does not fall during normal pregnancy, as would be expected in response to PVE [20, 21]. Furthermore, the maternal vasculature is responsive to adrenergic receptor-mediated vasoconstriction, but *in vivo* and *ex vivo* experiments show

that this response is blunted in pregnant compared to non-pregnant women and experimental animals [22–24]. Studies have examined the temporal changes in SNA and mechanisms within the blood vessel wall that buffer SNA-mediated vasoconstriction during normal pregnancy.

Temporal changes in SNA during normal pregnancy.

Studies in humans indicate that SNA is increased early in normal pregnancy [17, 25]. Jarvis et al recruited 11 healthy women with no comorbidities and planning a pregnancy to conduct peroneal microneurography measurements for assessment of MSNA [17]. By 6 weeks of gestation, there was increased MSNA over pre-pregnancy values. Other investigators have begun to examine the time-dependent changes in SNA during pregnancy. Kuo et al utilized an indirect measurement of SNA, that is the low-/high-frequency power ratio of heart rate variability, to suggest that SNA is increased in the first trimester compared to non-pregnant women [26]. Moreover, they put forward that SNA progressively increases towards the second trimester and continues to rise in the third trimester. Several research groups have shown that SNA is increased in late pregnancy as well. Usselman et al detected high MSNA in microneurography experiments in 11 pregnant women (33 ± 1 weeks of gestation, 31 ± 1 years of age, and a pre-pregnancy BMI of 23.5 ± 0.9 kg/m²) compared to 11 non-pregnant control women (29 ± 1 years old and a BMI of 25.2 ± 1.7 kg/m²) [27]. Similar results were obtained by Charkoudian and colleagues at this gestational age [28]. In another study, Schmidt et al examined the burst frequency (bursts/minute) incidence (bursts/100 heartbeats) of the peroneal nerve in normal pregnant women (N=10) at 33 ± 5 weeks of gestation and non-pregnant (N=13) women between the ages of 18 and 40 yr with normal cardiovascular and metabolic parameters [29]. The burst frequency and incidence were higher in the pregnant group. This team of researchers also found that the number of action potentials within individual bursts were similar between groups, which suggests that there was no difference in individual firing of neurons within bursts of integrated sympathetic activity. They concluded that increased neuronal multiunit bursts mediate the elevated SNA. Such studies have fueled interest in examining mechanisms whereby SNA is increased during normal pregnancy.

Mechanisms of increased SNA during normal pregnancy.

Although human studies have repeatedly demonstrated that there is increased SNA during normal pregnancy, the mechanisms behind this are not yet fully understood. Interestingly, the study mentioned above by Jarvis and colleagues examined the magnitude whereby upright tilt increases MSNA in order to determine the extent that arterial baroreceptor unloading and vagal withdrawal contributes to sympathetic stimulation in early pregnancy [30]. The magnitude of this response was similar between pre-pregnancy and pregnant time points; this indicated that mechanisms of reduced baroreceptor sensitivity were not responsible for early increases in SNA, which is also thought to occur in late pregnancy [31]. As changes in baroreceptor sensitivity do not seem to mediate the increased SNA during normal pregnancy, it was suggested that this increase stems from reduced central mechanisms of baroreflex gating and resulting in increased sympathetic outflow [32]. In order to examine the central mechanisms mediating increased SNA during normal pregnancy, experimental animal models have been utilized.

Studies in pregnant animal models support the human literature that SNA is increased during normal pregnancy [33]. Moreover, such models have been utilized to delve deeper into the mechanisms mediating the increased SNA during normal pregnancy. It was shown that the hypothalamus plays a role in the increased sympathetic drive during pregnancy in rats. Acute inhibition of outflow from the hypothalamus in the area of the arcuate nucleus (ArcN) reduces blood pressure to a greater extent in anesthetized, near-term pregnant versus non-pregnant rats [19]. Although this was not associated with greater reductions in heart rate, it was accompanied by greater reductions in lumbar, splanchnic, and renal SNA in the pregnant group. ArcN-mediated control of the cardiovascular system is mediated by interactions with several brain regions, including the paraventricular nucleus (PVN) and the rostral ventrolateral medulla (RVLM) [34]. In the PVN, while GABAergic-mediated inhibition of neuronal signaling participates in arterial baroreflex-mediated sympathoinhibition in non-pregnant female rats, there are reductions in SNA inhibitory mechanisms in this brain region by the end of pregnancy in rats [35, 36]. Pregnancy impairs baroreflex control of heart rate in rats and during late gestation in rabbits via insulin resistance [37, 38], which may contribute to the reduced baroreflex-dependent GABA control of heart rate while blood pressure falls during normal pregnancy. In contrast, increased baroreflex-independent GABAergic-mediated inhibition is found to control RSNA and blood pressure during pregnancy [39]. It is known that the ArcN and PVN project into the RVLM and regulate RSNA [40], but these neuronal connections have not been fully explored in normal pregnancy. Nevertheless, acute studies using administration of the GABA receptor antagonist, bicuculline, directly into the RVLM in sinoaortic denervated, near-term pregnant rats increased baroreflex-independent GABAergic inhibition of RSNA and blood pressure [39]. Specifically, this acute microinjection of bicuculline increased mean arterial blood pressure in non-pregnant rats by ~80 mmHg and pregnant rats by ~110 mmHg. The greater response in pregnant rats was partially mediated by angiotensin (ang) II-angiotensin type 1 receptor signaling [39]. These mechanisms for resetting baroreceptor function may help to protect against blood pressure changes in pregnancy during progressive uterine distention, which elicits increases in plasma renin activity (PRA), the rate-limiting enzyme in ang II production [41, 42]. In summary, these data suggest that during normal pregnancy, 1) central mechanisms are increased in the PVN that direct SNA toward appropriate control of heart rate as blood pressure falls; 2) the RVLM restrains or withdraws SNA targeting of the cardiovascular system; 3) whereas, there is increased ArcN-mediated control of peripheral vascular tone.

Mechanisms to buffer SNA-mediated control of maternal hemodynamics during normal pregnancy.

It seems as if there are central mechanisms that alter SNA drive to the vasculature. Even though sympathetic drive is increased during normal pregnancy, it is suggested that the maternal vasculature actively mounts mechanisms to buffer exaggerations in SNA-mediated vasoconstriction. This likely mediates the dissociation between the increased sympathetic outflow and the overall maternal vasodilation that is typically observed during normal pregnancy, which is referred to as reduced neurovascular transduction. Neurovascular transduction is calculated by dividing vascular resistance by MSNA to provide an estimate of sympathetic signaling to control vascular tone [43]. The formula was applied using

reduced forearm vascular resistance and increased MSNA found in normal pregnant cohort at around 6 weeks of gestation and the result being lower sympathetic vascular transduction [17]. Usselman et al found a lower value for this parameter in later gestation at 33 ± 4 weeks utilizing values for total peripheral resistance normalized to MSNA [32]. This lower value suggests that maternal blood vessels have mechanisms to blunt vasoconstriction in the face of increased SNA during normal pregnancy. This is supported by rat studies, including those cited above where, even though blood pressure was lower during normal pregnancy, there was a greater fall in blood pressure following inhibition of central SNA outflow. These data suggest that there is an important balance between SNA and vascular mechanisms to allow for appropriate vasodilation and blood pressure regulation during normal pregnancy.

An important circulation in pregnancy is that of the uterus and placenta. A larger fraction of cardiac output is directed toward the uteroplacental circulation in normal pregnancy to support the growth of the fetal-placental unit [44, 45]. Uterine artery blood flow is greater in near-term pregnant over non-pregnant rabbits [46]. To examine whether this was mediated by blunted responsiveness to sympathetic drive, exercise was utilized as a physiological inducer of SNA. Exercise reduced uterine blood flow in non-pregnant rabbits, and this response was attenuated in the pregnant group. Similar findings were found in rats [47, 48]. These studies indicate that the uterine vasculature upregulates mechanisms to temper the impact of increased SNA during pregnancy on vascular tone [49]. To more closely examine such mechanisms, the function of individual adrenergic receptors and their control of uterine vascular tone during pregnancy have been assessed. In pressurized uterine arteries from late-pregnant rats, there is increased α_1 -adrenergic receptor-induced vasoconstriction and α_2 -mediated relaxation whereas, there is reduced β -receptor-mediated relaxation [50]. The increased α_2 -mediated vasorelaxation was dependent on the endothelium and nitric oxide synthase (NOS). Several studies in isolated uterine arteries from pregnant humans and various experimental animal models [51–57] have demonstrated that endothelium-dependent and independent pathways play increased roles in buffering adrenergic receptor-induced vasoconstriction in pregnant versus non-pregnant groups. These enhanced vasodilatory and vasoconstriction-buffering mechanisms are mediated by increased NOS, vascular smooth muscle cell responsiveness to vasodilators, and reduced capacity of the smooth muscle layer to depolarize [54, 58]. Out of these mechanisms, there is a considerable amount of evidence supporting the importance of NOS in the endothelium to promote vasorelaxation and buffering of vasoconstriction during pregnancy [59–64]. For example, the typical blood pressure fall occurring in normal pregnancy is prevented by administration of the non-selective NOS inhibitor, L-NAME, during the last week of pregnancy in rats [65]. Moreover, NOS inhibition produces greater hypertension in pregnant versus age-matched, non-pregnant rats implicating increases in NOS-mediated control of vascular function and blood pressure during normal pregnancy. However, whether NOS inhibition-mediated increases in vasoconstriction and blood pressure are dependent on increased SNA signaling *in vivo* is understudied. Collectively, these *ex vivo* and *in vivo* studies implicate endogenous changes in α - and β -adrenergic receptor function in control of vascular tone during pregnancy via downstream signaling moderators, like NOS. NOS seems to play a greater role than other moderators, like vasodilatory prostaglandins, in the chronic control of maternal blood pressure during normal pregnancy [66, 67].

Importance of pregnancy-related factors in modulating SNA-mediated control of vascular function and blood pressure during normal pregnancy.

Regarding the mechanisms of continued vasodilation and activation of NOS to control maternal hemodynamics throughout gestation, there are several pregnancy-related factors involved. The upregulation of these mechanisms is thought to rely on increases in circulating pregnancy hormones, like progesterone, placental growth factor (PlGF), and/or relaxin [62]. By 6–7 weeks of pregnancy in humans, there are increases in the pro-angiogenic and pro-vasodilatory factor, PlGF [68]. This is supported in other studies where rises in circulating and urinary levels of PlGF occur from 8–12 weeks to maximum by 29–33 weeks [32, 69]. In contrast, serum vascular endothelial growth factor (VEGF) levels do not change dramatically throughout the course of normal gestation [70]. But it is important to note that PlGF is thought to promote vasodilation by increasing VEGF signaling due to the ability of PlGF to bind with high affinity to VEGFR1 whereas, VEGF binds both VEGFR1 and VEGFR2 [71]. Cooperatively, this allows for increased VEGF signaling through the VEGFR2 receptor to activate vascular NOS [72].

To examine the impact that proper angiogenic signaling on control of vascular function and blood pressure regulation during normal pregnancy, experiments in rodents to quench PlGF and VEGF levels have been performed. Chronic infusion of sFlt-1 or adenoviral-mediated overexpression of sFlt-1 in once normotensive pregnant rats and mice produces hypertension and reduces the levels of angiogenic factors [73–75]. Although SNA was not examined, sFlt-1 infusion in pregnant rats is associated with increased phenylephrine (Phe)-induced vasoconstriction in isolated vascular preparations of aorta, carotid, mesenteric arteries, and renal artery [76]. As this model is linked to hypertension due to reductions in NO bioavailability [75], it is likely that sFlt-1 reduces the ability of VEGF and PlGF to stimulate NOS, which effectively reduces the capacity of this enzyme system to buffer SNA-mediated vasoconstriction. Therefore, it seems that appropriate angiogenic balance allows for buffering of SNA-induced vasoconstriction for proper control of vascular tone and blood pressure regulation during normal pregnancy.

Regarding relaxin, there are early and continued rises in relaxin levels during pregnancy [77–79]. In human subcutaneous arteries and rat and mice small renal arteries, relaxin mediates the ability of VEGF and PlGF to buffer vasoconstriction [80]. These studies utilized arteries isolated under non-pregnant conditions. Whereas, Marshall et al report that pregnancy-induced adaptations of blunted ang II- and Phe-induced vasoconstriction are attenuated in first-order branches of the superior mesenteric artery isolated from pregnant relaxin-deficient compared to wild-type mice [81]. Others have found that relaxin mediates increases in uterine blood flow during pregnancy [82]. These findings led investigators to uncover that pregnancy-induced increases in relaxin promote VEGF and PlGF signaling in the arterial wall [80]. Indeed, these factors act together leading to endothelial cell production of the peptide, endothelin (ET)_{1–32}, which acts in an autocrine manner to stimulate the vasodilatory endothelin receptor type B (ET_B) and subsequent stimulation of NOS [83]. Furthermore, these studies showed that α -adrenergic receptor-mediated vasoconstriction is buffered by relaxin. Although it has not been explored *in vivo* whether this vasodilatory pathway buffers SNA control of vascular tone and blood pressure in regulation during

pregnancy, the aforementioned studies suggest that may be the case. In addition, studies suggest that relaxin may act to regulate SNA-mediated control maternal hemodynamics via signaling in the brain. Injection of relaxin into the subfornical organ (SFO) in anesthetized, non-pregnant, and arterial baroreceptor-denervated female rats resulted in activation of spinally projecting neurons in the PVN and increases SNA and MAP [84]. As the SFO does not have a blood-brain barrier [85], this suggests that circulating relaxin can stimulate blood pressure regulatory centers in the brain. In contrast to these studies in non-pregnant female rats, the ability of acute intravenous infusion of relaxin to increase blood pressure is attenuated as pregnancy progresses in anesthetized rats, with no blood pressure effect detected by term [86]. As relaxin receptor mRNA levels in the SFO are not different between late-pregnant and non-pregnant rats [84], there are potential implications for studying the mechanisms regulating downstream signaling pathways by the relaxin receptor in the brain. Therefore, pregnancy-related factors have the ability to directly impact the brain and peripheral vasculature to mediate proper control of vascular function and blood pressure regulation during normal pregnancy. Future studies should determine the relative contribution of pregnancy-related factors in central neural pathways versus direct systemic actions on modulating SNA-mediated control of vascular tone, including proper perfusion of the uteroplacental unit and blood pressure regulation during normal pregnancy.

In summary, these findings suggest that alterations in mechanisms buffering adrenergic receptor-mediated vasoconstriction and encouraging central mechanisms of SNA and peripheral vasoconstriction during normal pregnancy have deleterious outcomes on the maternal cardiovascular system. This includes exaggerated vasoconstriction in the uterus to elicit placental ischemic events with resulting endothelial and vascular dysfunction in promoting the hypertension in PE.

SNA in PE

PE is estimated to affect up to 1 in 20 pregnancies in America [87]. Worldwide, 10 million women are estimated to develop this disorder and ~75,000 maternal and ~500,000 neonatal deaths per year are attributed to hypertensive disorders of pregnancy [88]. Hypertensive disorders of pregnancy are a leading cause of maternal and perinatal morbidity and mortality [89, 90]. PE not only poses an immediate risk for the mother and fetus but also predisposes both parties to increased cardiovascular disease risk later in life [91]. As the only steadfast 'cure' for PE is delivery of the fetus and placenta, a heavy emphasis is placed on the need for preclinical research to fully elucidate the pathogenesis of PE in order to develop novel treatment strategies. This is especially true as the goal of current prophylactic strategies is to slow its progression and prolong the pregnancy, thus serving as management purposes and not necessarily curing the disorder [92]. These prophylactic agents include nifedipine (calcium channel blocker), hydralazine (non-specific vasodilator), labetalol (dual α_1 - and non-selective β -adrenergic receptor antagonist), methyldopa (α_2 -adrenergic receptor agonist), or magnesium sulfate to prevent seizures if the disorder progresses to eclampsia. In the occurrence of acute-onset, severe hypertension during pregnancy or in the post-partum period, intravenous labetalol and hydralazine are considered first-line medications [93]. These drugs are intended to block mechanisms of vasoconstriction or to antagonize SNA [94]. Therefore, this supports that

SNA plays a role in the pathogenesis of PE, and optimizing such strategies against these pathways could be key to treating this maternal disorder. Further credence for targeting SNA in the treatment of PE is that SNA is elevated during this maternal disorder and spinal anesthesia with the nerve blocker, bupivacaine was able to significantly reduce blood pressure in severely preeclamptic patients at the time of cesarean delivery [95, 96]. Understanding how to most effectively antagonize SNA in PE may lead to the discovery of a cure for this hypertensive disorder of pregnancy, as downsides of current management strategies include that oral nifedipine is not effective in all patients [94]; labetalol has side effects of headache and tachycardia [97]; and prolonged treatment with hydralazine can cause lupus-like symptoms [98]. This section of the review will focus on elevated SNA in the pathophysiology of PE, but future studies should more deeply examine the parasympathetic nervous system, as increased heart rate variability in PE seems to be mediated by reductions in the latter [99, 100].

Elevated SNA in PE.

There have been several observational studies supporting that SNA is elevated in PE. In 1957, Raab suggested that exaggerations in the blood pressure response to norepinephrine (NE) infusion in the 13th week of gestation in human is predictive of PE [101]. It was later reported that pregnant women destined for PE have greater blood pressure responsiveness to the cold pressor test [102]. In 1977, Zuspan observed that there are alterations in SNA by measuring urinary NE levels in PE and eclampsia in humans [103]. However, such assessments do not allow for reliable measurements of the sympathetic drive to peripheral organ systems, as a significant amount of monoamines that are filtered at the glomerulus are not detected in the urine [104]. Additional studies have reported other measures of SNA to be increased in PE, including heart rate and blood pressure variability and responses to postural alterations, low frequency (LF)/high frequency (HF) ratio of heart rate, baroreflex sensitivity, and phase difference at LF calculated by spectral analysis from continuous recordings of heart rate and blood pressure from finger pulse waves [99, 105–107]. Investigators have measured MSNA to assess sympathetic drive in PE. One of the first studies examining MSNA in PE detected increases in preeclamptic patients compared to normotensive pregnant, normotensive non-pregnant, and hypertensive non-pregnant women (Figure 1), which is significantly attenuated after delivery [108]. Subsequent studies presented similar findings [105, 109]. These data implicate that elevations in SNA-mediated vasoconstriction promote the pathogenesis of PE, but experimental evidence is needed to determine the central mechanisms allowing for increased SNA signaling in the maternal cardiovascular system and whether it has a causal role in promoting this maternal disorder.

Linking elevated SNA, placenta ischemic events, and hypertension in PE.

Studies in experimental animal models have begun testing the hypothesis that elevated SNA promotes hypertension during pregnancy. A PE-like phenotype is induced by stimulation of SNA with cold and fasting stressors in pregnant rats [110]. Moreover, stress-induced by acute isolation decreases uterine blood flow in pregnant sheep via α_1 -adrenergic receptor signaling [111]. Thus, chronic encounters with stressful situations may foster placental ischemic/reperfusion events. This is intriguing, as placental ischemic/reperfusion events are thought to mediate the release of soluble placental factors, which promote cardiovascular

abnormalities and hypertension in PE. This has been shown in animal models of placental ischemia or hypoxia exposure. For example, surgical-induced Reduced Uterine Perfusion Pressure (RUPP) in rats on gestational day 14 results in hypertension and lower glomerular filtration rate (GFR) and renal plasma flow (RPF) by day 19 (Figure 2) [15, 112]. These hemodynamic responses are indicative of increased vasoconstriction mechanisms in the kidney and renal mechanisms of hypertension [113]. Combined α - and β -adrenergic receptor blockade in RUPP brings blood pressure down to similar levels in normal pregnant rats [114]. These data suggest that placental ischemia-induced hypertension is mediated by increased SNA and adrenergic receptor-induced vasoconstriction. However, a limitation of using surgical- or hypoxia-induced placental ischemic models of PE is the inability to assess mechanisms that contribute to early alterations in placental vascular remodeling, vascular resistance, and ischemia/hypoxia. In this regard, the data using such models should be interpreted with caution, but this work highlights the importance of studying placental ischemia and soluble factors in the pathogenesis of PE. Therefore, these placental ischemic pathways should be examined in animal models exposed to environmental stress, such as those mentioned above, during early pregnancy to identify whether early elevations in SNA promote the directional mechanism whereby placental ischemia leads to vascular dysfunction and maternal hypertension in PE.

Interactions between placental ischemic factors and SNA in mediating vasoconstriction and hypertension in PE.

Aberrant elevations SNA during pregnancy may lead to placental ischemia, and there is also evidence that factors released from the ischemic placenta may allow for SNA-mediated vasoconstriction to promote placental ischemia-induced hypertension in PE. Utilizing RUPP rats and other models, it was shown that placental ischemia/hypoxia elicits the release of pro-hypertensive factors into the maternal circulation [115]. This circulating milieu is characterized by increased antiangiogenic factors, like sFlt-1, which target and quench bioavailable VEGF and PlGF, and pro-inflammatory factors, like TNF- α and AT1-AA [116]. Therefore, the vascular dysfunction occurring in response to the pro-hypertensive milieu of placental ischemia may potentiate SNA-mediated vasoconstriction and hypertension in the pathogenesis of PE.

It is known that PlGF is lowest in those pregnancies with PE and intrauterine growth restriction (IUGR), which is a fetal complication of this disorder [69, 117, 118]. Studies showed that PlGF and vascular NOS function are reduced in placental ischemia-induced hypertension and resulting in greater vasoconstriction capacity, including the response to Phe (Figure 3) [119, 120]. Administration of PlGF prevents placental ischemia-induced hypertension in RUPP rats [15] along with increasing endothelial- and NOS-dependent buffering of Phe vasoconstriction and endothelial- and NOS- dependent relaxation RUPP in rats [76]. RUPP rats have greater Phe-induced vasoconstriction in aorta, carotid, mesenteric, uterine, and renal arteries [76, 114, 121].

Pro-inflammatory mechanisms also have a role in promoting the vascular dysfunction and hypertension in PE. There is evidence of increased populations and activation of CD4⁺ T helper lymphocytes in preeclamptic women [122, 123]. Experimentally, adoptive transfer of

CD4⁺ cells from RUPP rats into once normotensive pregnant rats demonstrated the direct pro-hypertensive role for this immune cell type. This maneuver increased blood pressure and circulating TNF- α and sFlt-1 levels [124, 125]. CD4⁺ cells also activate autoantibody-producing B lymphocyte cells, with the most well-studied of these autoantibodies, the AT1-AA, eliciting reductions in GFR and RBF, increases in renal vascular resistance (RVR), and hypertension in pregnant rats via increasing sensitization to ang II [126]. Although it is unknown if AT1-AA or ang II modulates SNA-mediated vasoconstriction during pregnancy, observations show that ang II signaling increases electrical field stimulation (EFS)-mediated vasoconstriction in mesenteric arteries from non-pregnant rats [127]. In humans, ang II infusion increases plasma NE levels during pregnancy [103]. Whether AT-AA or ang II actions in modulating SNA control of vascular tone and hypertension during PE pregnancy should be examined, which includes utilizing models with placental ischemia-induced hypertension that have increased ang II-mediated vasoconstriction and hypertension [128, 129].

Another potent vasoconstrictor system in the pathogenesis of placental ischemia-induced hypertension is endothelin (ET)-1 production in the blood vessel wall [130]. ET-1 production from endothelial cells is increased in PE [131]. *In vitro* studies show that placental ischemic factors or RUPP serum increase ET-1 release from human glomerular endothelial cells [131]. *In vivo*, antagonism of vasoconstrictive ET type A (ET_A) receptors abolished RUPP-induced hypertension [132]. During endothelial dysfunction and hypertensive disorders, like PE, ET_A-mediated vasoconstriction goes unbalanced perhaps as a result of attenuated contribution of endothelial ET_B receptor-mediated stimulation of NOS and vasodilation [130]. Curiously, in male ET_B-deficient rats lacking these receptors everywhere except adrenergic nerves, while still expressing ET_A receptors on vascular smooth muscle, the ET_B agonist sarafotoxin c (S6c) produced a dose-dependent pressor response [133]. This was reversed by the α_1 -adrenergic receptor antagonist, prazosin, and augmented by the β -adrenergic receptor antagonist, propranolol. Renal denervation was able to reduce blood pressure in these rats [134]. Activation of ET_B receptors increases superoxide levels that may activate sympathetic ganglia and SNA *in vivo* [135]. The relative contribution of pro-hypertensive effects of ET_B receptors on nerves versus ET_A receptors on vascular smooth muscle, and whether there is any influence of reduced vasoconstrictive buffering capacity of vasodilatory ET_B receptors on endothelial cells, during the development of placental ischemia-induced should be researched. This includes the relative role of mechanisms, including placental ischemic factors, ET-1, and SNA. These pathways may collectively contribute to the integrative nature of the pathogenesis of hypertension in PE.

The integrative nature of hypertension in PE.

As the above studies imply, hypertension in PE is driven by combined actions of placental ischemic factors and downstream activation of vasoconstriction pathways, such as ET-1 and SNA. Placental ischemic factors, like sFlt-1, TNF- α , and AT1-AA, induce hypertension in pregnant rats via ET_A signaling [136]. Although the impact of SNA in modulating this response is unknown, there is evidence accumulating that it plays a role. First, *in vitro* data suggest that circulating factors promote elevations of SNA in PE whereby treatment with

10% or 50% plasma from preeclamptic women elicits greater NE release in isolated sympathetic nerves from chicken embryos compared to normotensive pregnant, hypertensive non-pregnant, or normotensive non-pregnant women [137]. This release of NE was attenuated with bupivacaine-mediated blockade of SNA. Furthermore, levels of neuropeptide Y (NPY), which is a potent vasoconstrictor produced during increased SNA, are elevated in the plasma of patients with PE at admission and decreased at 6 days postpartum [138]. It is unclear whether placental ischemic factors are responsible for the increased SNA found in PE and the contribution of downstream vasoconstrictor substances, like NPY, on control of vascular tone and blood pressure in promoting placental ischemia-induced hypertension. Second, data suggest that agonistic autoantibodies are produced that activate the α -adrenergic receptor, which are detected in over half of the refractory hypertensive patients [139]. Infusion of these antibodies increases blood pressure in anesthetized rats and promotes vasoconstriction, and these effects are abolished by prazosin in *ex vivo* artery preparations [140]. Studies should examine whether chronic infusion of these autoantibodies elicits hypertension in experimental model of pregnancy or if their blockade prevents placental ischemia-induced hypertension. Third, studies implicate an interaction between ET-1 and SNA in mediating hypertension, but this has not been assessed in PE. In male rats, ET-1 potentiates NE-induced vasoconstriction in mesenteric arteries [141]. As a caveat, lower doses of ET-1 attenuate NE release and the pressor response to sympathetic nerve stimulation in these arteries, whereas higher doses of ET-1 increase the pressor response [142].

Summary and clinical perspectives

The goal of understanding the pathogenesis of PE is to assist in identifying and optimizing rapidly effective and inexpensive therapies to treat this maternal disorder. This is necessary for several reasons. The occurrence of PE is increasing [143]; maternal mortality is on the rise with PE being a significant contributor [144]; hypertension and vascular dysfunction in preeclamptic women is not always sufficiently controlled by available prophylactic agents [145, 146]; and women with a previous hypertensive pregnancy have greater risk for future cardiovascular disease as they age [147–149]. As detailed in this review, preclinical animal models are assisting in a better understanding of the pathogenesis of PE. Such models support that placental ischemia and hypoxia elicit the release of pro-hypertensive factors from the placenta, including pro-inflammatory and anti-angiogenic factors. Once in the maternal circulation, they disrupt vascular tone homeostasis by reducing levels of vasodilators, like NO, and induce endothelial activation and production of the most potent endogenous vasoconstrictor known, ET-1. This allows for vasoconstriction, reduced renal hemodynamics, and hypertension. Intriguingly, experimental animal and human studies have detected overactivation of the SNA in PE, but its role in the development of PE is unclear.

It is hypothesized that overactivation of the SNA mediates the development of PE, but the exact mechanisms of how this occurs are largely unexplored. As mentioned in this review, there are several steps whereby SNA could contribute to placental ischemia-induced hypertension. Foremost, early and chronic exaggerations in SNA and the inability of the uterine circulation to fully compensate for this could facilitate the development of placental ischemia/reperfusion events. Placental ischemia and hypoxia result in the release of pro-

hypertensive placental factors into the mother's circulation and the onset of hypertension. These soluble factors may induce hypertension by stimulating SNA and increasing its signaling. For instance, placental ischemic factors could directly induce activation of the SNA by central mechanisms. They could also exaggerate SNA-mediated signaling in the blood vessel wall. As these placental factors reduce the vasodilatory and vasoconstriction-buffering capacity of NO, this would lead to increased adrenergic receptor-induced vasoconstriction in the face of an overactive sympathetic nervous system in PE. Additionally, these ischemic factors promote ET-1-induced vasoconstriction and evidence suggests this pathway could synergize with an overactive SNA to exaggerate vasoconstriction in PE. Figure 4 illustrates each of these steps in the hypothetical scheme that placental ischemia-induced activation of the SNA exaggerates placental ischemia-vasoconstriction and hypertension. Whether differential activation of these mechanisms contributes to the complexity of the clinical manifestations of PE is worth studying. Moreover, the relative contribution of each of these placental, brain, and systemic vascular pathways should be teased apart to help determine if development of safe therapies targeted toward any of these systems can advance treatment strategies to avoid the deleterious impact of PE. There is promising evidence of targeting altered angiogenic balance to increase PlGF [15]; anti-inflammatory treatments [150]; promoting NO-mediated vasorelaxation and vasoconstriction buffering capacity with phosphodiesterase (PDE)5 inhibitors or other compounds to amplify NO/cGMP signaling [151]; blockers to attenuate ET-1/ET_A signaling [152]; or combined prophylactics. This review also implicates that development of agents and treatment strategies to lower central and peripheral mechanisms of SNA and signaling should also be a focus in PE research.

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Abbreviated Definitions List

Ang II	angiotensin II
AT1-AA	angiotensin type 1 receptor autoantibody
AT1R	angiotensin type 1 receptor
EFS	electrical field stimulation
ET-1	endothelin-1
GABA	gamma-aminobutyric acid
GFR	glomerular filtration rate
IUGR	intrauterine growth restriction
LF/HF	low frequency/high frequency power
L-NAME	L-N ^G -Nitroarginin methyl ester

MAP	mean arterial blood pressure
MSNA	muscle sympathetic nervous activity
NO	nitric oxide
NOS	nitric oxide synthase
NPY	neuropeptide Y
PDE	phosphodiesterase
PIGF	placenta growth factor
PRA	plasma renin activity
PVE	plasma volume expansion
PVN	paraventricular nucleus of the hypothalamus
RPF	renal plasma flow
RUPP	reduced uterine perfusion pressure
RVLM	rostral ventrolateral medulla
RVR	renal vascular resistance
S6c	sarafotoxin 6c
sFlt-1	soluble fms-like tyrosine kinase-1
SNA	sympathetic nerve activity
TNF-α	tumor necrosis factor-alpha
VEGF	vascular endothelial growth factor
VEGFR1	vascular endothelial growth factor receptor 1 (Flt-1)
VEGFR2	vascular endothelial growth factor receptor 2 (KDR/Flk1)

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Figure 1.

Mean arterial pressure (top) and multiunit recordings of postganglionic muscle sympathetic nerve activity expressed as bursts/minute (middle) or corrected for heart rate and expressed as burst/100 heartbeats (bottom). NN = normotensive non-pregnant (N=6, 25±1 years old); HN = hypertensive non-pregnant (N=7, 27±2 years old); NP = normotensive pregnant (N=8, 26±1 years old, 32±1 weeks of gestation); PE = preeclamptic (N=9, 26±1 years old, 33±1 weeks of gestation). Mean±SEM, *P<0.05 vs. respective non-pregnant or pregnant normotensive control. Adapted from ref [108].

Figure 2.

Top: Mean arterial pressure, middle: glomerular filtration rate, and bottom: renal plasma flow in the reduced uterine perfusion pressure (RUPP) model of placental ischemia-induced hypertension vs. normal pregnant controls at gestational day 19. Adapted from ref [112].

Figure 3.

Top: Cumulative concentration-response curves to phenylephrine (Phe)-induced vasoconstriction in mesenteric arteries isolated from the reduced uterine perfusion pressure (RUPP) model of placental ischemia-induced hypertension at gestational day 20 in the presence or absence of the non-selective inhibitor of NOS, L-NAME (100 μM). Bottom: Depiction of $-\log EC_{50}$ (sensitivity) to Phe responses above. $N=5-9/\text{group}$, mean $\pm$ SEM, two-way ANOVA inset. Adapted from ref [120].

Figure 4.

Hypothetical scheme whereby the sympathetic nervous system activity (SNA) contributes to placental ischemic/reperfusion events. Moreover, this figure illustrates steps in the hypothesis that placental ischemia-induced activation of the SNA mediates vasoconstriction and hypertension. The relative contribution of each of these placental, brain, and systemic vascular pathways should be teased apart to determine whether they mediate the pathogenesis of PE and if development of safe therapies targeted toward any of these systems can advance treatment strategies to avoid the deleterious impact of this maternal

disorder. Asterisks represent promising evidence of targeting altered angiogenic balance to increase PlGF [15]; anti-inflammatory treatments [150]; promoting NO-mediated vasorelaxation and vasoconstriction buffering capacity with phosphodiesterase (PDE)5 inhibitors or other compounds to amplify NO/cGMP signaling [151]; blockers to attenuate ET-1/ET_A signaling [152]; or combined prophylactics. Development of agents and treatment strategies to lower central and peripheral mechanisms of SNA activation and signaling should also be a focus in PE research.

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