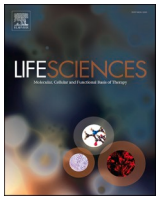
Life Sciences 320 (2023) 121351

Contents lists available at ScienceDirect

Life Sciences

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



Role of blood-borne factors in sympathoexcitation-mediated hypertension: Potential neurally mediated hypertension in preeclampsia

Abdoulaye Issotina Zibrila [a,b], Zheng Wang [c], Machioud Maxime Sangaré-Oumar [b], Ming Zeng [a], Xiaoxu Liu [a], Xiaomin Wang [a], Zhaoshu Zeng [a], Yu-Ming Kang [a,*], Jinjun Liu [a,**]

[a] Department of Physiology and Pathophysiology, Xi'an Jiaotong University School of Basic Medical Sciences, Key Laboratory of Environment and Genes Related to Diseases, Xi'an 710061, Shaanxi, PR China
[b] Department of Animal Physiology, Faculty of science and Technology, University of Abomey-Calavi, 06 BP 2584 Cotonou, Benin
[c] Key Laboratory of Shaanxi Province for Craniofacial Precision Medicine Research, College of Stomatology, Xi'an Jiaotong University, PR China

ARTICLE INFO

Keywords:
Hypertension
Neurally mediated hypertension
Preeclampsia
Placental derived pro-hypertensive factors

ABSTRACT

Hypertension remains a threat for society due to its unknown causes, preventing proper management, for the growing number of patients, for its state as a high-risk factor for stroke, cardiac and renal complication and as cause of disability. Data from clinical and animal researches have suggested the important role of many soluble factors in the pathophysiology of hypertension through their neuro-stimulating effects. Central targets of these factors are of molecular, cellular and structural nature. Preeclampsia (PE) is characterized by high level of soluble factors with strong pro-hypertensive activity and includes immune factors such as proinflammatory cytokines (PICs). The potential neural effect of those factors in PE is still poorly understood. Shedding light into the potential central effect of the soluble factors in PE may advance our current comprehension of the pathophysiology of hypertension in PE, which will contribute to better management of the disease. In this paper, we summarized existing data in respect of hypothesis of this review, that is, the existence of the neural component in the pathophysiology of the hypertension in PE. Future studies would address this hypothesis to broaden our understanding of the pathophysiology of hypertension in PE.

1. Introduction

Hypertension, defined by elevated blood pressure (BP >140/90 mmHg), is a life-threatening cardiovascular disease concerning a third of the world population with higher proportion in low- and middle-income countries [1]. Despite intensive investigations in the field, the exact cause of hypertension in most patients populating clinics is still elusive [2]. Thus, the majority of these patients develop the primary hypertension in contrast to patients whose hypertension is a consequence of an underlying condition such as pheochromocytoma or renal artery stenosis [3,4]. However, number of contributing factors to the progression or worsening of the hypertension have been documented in human and their contributing role to the onset of hypertension has been demonstrated in animal models. These factors include but not limited to unbalanced diet with high sodium chloride and low potassium, alcohol consumption, lack of physical activities and obesity, age [1,2], infections [5] and exposures to environmental pollutants [6,7]. Animal models helped understand some pathophysiological aspects of human hypertension and the development of pharmacological interventional tools [2]. In addition to early remarks on the potential neurogenic component of hypertension in patients with resistant hypertension [8], recent investigations demonstrating the therapeutical potential for renal denervation and the association between psychosocial factors and hypertension substantially support the idea of neurally mediated hypertension [9–11]. Currently, the sympathetic overactivation is regarded as the main neurogenic component of hypertension. Both patients and several animal models present increased sympathetic nerve activity (SNA) usually evidenced by elevated circulating NE level, which witness the state of sympathetic outflow toward the kidney [12,13]. Investigations concerning the mechanism and role of increased SNA in

* Correspondence to: J. Liu, No.76 Yanta West Road, School of Basic Medical Sciences, Health Science Center, Xi'an Jiaotong University, Xi'an 710061, Shaanxi, PR China.
** Correspondence to: Y.-M. Kang, No.76 Yanta West Road, Department of Physiology and Pathophysiology, Xi'an Jiaotong University School of Basic Medical Sciences, Key Laboratory of Environment and Genes Related to Diseases (Xi'an Jiaotong University), Ministry of Education, Xi'an 710061, PR China.
E-mail addresses: ykang@mail.xjtu.edu.cn (Y.-M. Kang), jupet.1128@mail.xjtu.edu.cn (J. Liu).

https://doi.org/10.1016/j.lfs.2022.121351
Received 29 September 2022; Received in revised form 19 December 2022; Accepted 27 December 2022
Available online 30 December 2022

hypertensive animal models have been reported [14] and interactions between genetic, psychological and hormonal factors among others, with stimulating input signal of peripheral origin has been suggested to cause increased SNA [13]. Number of peripheral factors, in addition to their vasoactive properties, is shown to interact with neural system and promote sympathetic overactivation. These factors include components of RAAS and immune soluble factors such as cytokines [15]. The hypothalamic paraventricular nucleus (PVN) and the nucleus of the solitary tract (NTS) are important autonomic function modulating centers with cardiovascular relevance. These nuclei integrate both neural and chemical signals, emanating from other regions of the brain especially the circumventricular organs (CVOs), to produce a pro-hypertensive sympathetic outflow to the spinal cord and the rostral ventrolateral medulla (RVLM) for the peripheral organs [16]. Because autonomic cardiovascular regulating centers are protected by the blood-brain barrier (BBB), the function of CVOs projecting to those centers should gain particular attention when analyzing the activity of those centers. This is important in a way, due to the lack of clear BBB at the CVOs level, CVOs, expressing receptors for many peripheral chemical signals, sense and relay these signals to centers such as the PVN or NTS [17,18].

As a hypertensive condition, preeclampsia (PE) is marked by new onset of increased BP beyond 140/90 mmHg and protein/creatinine ratio $\geq$ 0.3 after 20 weeks' gestation in response to placental ischemia [19,20]. This ischemia is believed to initiate the excessive production of numerous soluble factors found in circulation and within the central organ of PE, the placenta. Because these soluble factors subside with placental removal, we termed them placental derived pro-hypertensive factors (PDHFs). The pro-hypertensive effect of PDHFs has been extensively investigated. Inflammation, endothelial dysfunction and oxidative stress induced by the PDHFs were shown to underlie the hypertensive pathophysiology in PE [21,22].

An unmet scientific curiosity is that, by analogy with chronic hypertension, would the PDHFs own neural effect that may promote hypertension in PE? In this review, we summarized evidences in favor of the existence of neurogenic component of the hypertension in PE. Thus, after having gathered evidences on peripheral soluble factors-induced sympathetic overactivity and rise in BP in animal models for hypertension, we explored the existing data for the activity of some those factors in PE to propose that, most likely, the PDHFs in PE may possess a neurostimulating effect that would set the neurogenic component of hypertensive pathophysiology in PE.

2. Neurally mediated hypertension

To date, intensive investigations in both human and animal models have supported the crucial role played by the central nervous system in the pathophysiology of hypertension, a multifactorial condition. Beside the neural mechanism in the baroreflex control of BP, the sympathetic system has been shown, based on number of findings, to substantially promote the rise in BP, this, in response to changes occurring in autonomic centers [14,23]. Sometimes referred to as neurogenic hypertension, the neurally mediated hypertension is currently understood as the consequence of alterations in sympathetic neuroendocrine signaling resulting in rise in BP [23]. Although the term "neurogenic hypertension" does not imply that the brain is the principal and sole source of the hypertensive condition, the use of "neurally mediated hypertension" seems more appropriate [24] as number of circulating factors, such salt (NaCl), Angiotensin II, lipopolysaccharide (LPS) [25], cytokines [26] among others, have been shown to act directly or indirectly on neural tissue to promote sympathetic-driven hypertension. Accordingly, the idea, in the neural mechanism of hypertension, is that the increase in BP results from the action of a variety of agents on nervous system that alters the central sympathetic outflow promoting elevation in sympathoexcitation and hypertension [24,27]. Thus, peripheral factors interfering with afferent or efferent nerve fibers of cardiovascular regulating centers of the brain such as the PVN [16,28–30] and rostral ventrolateral medulla RVLM initiate and maintain a neurogenic vasoconstriction [31].

Different central and peripheral conditions/factors heighten the sympathetic activity emanating from several brain regions, known to control the cardiovascular function, which direct it to the peripheral effectors including kidney, arteries and heart. Those factors are wide in nature. From body morphological change, such as obesity, to electrolyte imbalance as induced by dietary salt, many factors or conditions could alter and set the sympathetic activity toward a pro-hypertensive trend. In a well detailed work, the effects of obesity and dietary salt on neurally mediated hypertension have been reviewed [23]. In addition, the influence of peripheral agents on neural activity including synaptic function and neuronal plasticity has been documented. For example, when peripheral inflammation is induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) in intestine (model of colitis), there was microglial activation associated with elevated Tumor necrosis factor-alpha (TNF-α) production and increased neural activity and excitability. This central effect was TNF-α dependent as TNF-α injection mimics the susceptibility to seizures induced peripherally through TNBS and its inhibition with TNF-α antibody prevented the increased susceptibility to seizures [32] suggesting that brain regions such as hippocampus respond to peripheral inflammation by increasing their neural excitability. When this occurs in brain regions with pre-sympathetic nerves, increased neural excitability would result in increased SNA. Moreover, peripheral Angiotensin II (AngII) was shown to break down the BBB, influence neural, and microglial activity in brain region with cardiovascular relevance resulting in sympathoexcitation and hypertension [33]. Exposure to environmental pollutants such as arsenic in food or drinking water [7] or Hexachlorobenzene (HCB), which can be found in environment as a by-product in several industrial processes [34] has been associated with increase in BP. In their review, Robert et al., summarized environmental factors shown to promote hypertension and although detailed mechanisms by which these factors affect BP are not fully understood, their effects have been largely attributed to their interaction with nervous system and vasculature [35]. Moreover, growing body of evidence suggests a link between infections such as malaria, cytomegalovirus infection, periodontal disease, chlamydia and helicobacter infections among others and the occurrence of hypertension. Today, the most common mechanism is chronic inflammation [5,36], which may trigger central deleterious effects. These evidences suggest that peripheral factors have ways to access different brain regions where they induce biological effects.

Hypertension is a multifactorial condition with different unknown (primary or essential hypertension) and known (secondary hypertension) underlying causes [3]. In animal models of both types of hypertension, the neural contribution to the progression of the disease was evidenced. In Spontaneously hypertensive rat (SHR), the model of human essential hypertension, imbalanced oxidant/antioxidant system in the RVLM marked by low antioxidant enzymes activity and increased $O_2^{\bullet -}$ or H_2O_2 level was shown to promote hypertension. Increasing the expression of antioxidant molecules SOD1, SOD2 or Catalase in the RVLM through viral microinjection attenuated the elevated mean arterial pressure (MAP) in this model [37]. Moreover, in a renovascular hypertension, a model for secondary hypertension, increased in oxidative stress in the PVN promoted hypertension through sympathoexcitation and central inhibition of ROS production with oligomeric proanthocyanidins improved the hypertensive condition [38,39]. All these evidences suggest that mechanisms of neurally mediated hypertension involve on one hand, stimulating agents (or factors) and on the other hand target molecular, cellular and structural components, which produce the "neurogenic order" of heightening of BP from the brain.

3. Circulating bioactive factors in neurally mediated hypertension

To understand the neural mechanism of hypertension, the effect of circulating factors on changes in neural tissue resulting in hypertension has been investigated. Experimental investigations have reported number of circulating bioactive factors acting on their targets to promote sympathetically – driven hypertension. The Table 1 summarizes the most commonly studied soluble factors in animal models.

3.1. Angiotensin II

As an important component of the RAAS, the contributory role of AngII to hypertension is reportedly well documented and supported by findings from several investigations [54,55]. Through the action on its type 1a receptor, the AT1aR, AngII causes hypertension by inducing vasoconstriction [56,57], promoting water and sodium retention through aldosterone and its downstream effects [45,48] and increasing the sympathetic overactivity [16,30,40–46]. In this section, evidence of the central effect of AngII, as circulating and centrally produced bioactive factor, promoting hypertension in animals will be discussed. Therefore, our focus will be about reports that involve investigations on central changes. The pro-hypertensive effect of AngII is primarily through AT1aR, which is supported by the anti-hypertensive effect of AT1 receptor blockers [54]. In addition to its direct effect on vessels and kidney [57–60], peripheral AngII acts centrally to promote hypertensive phenotype. Thus, subcutaneous AngII infusion induced pro-hypertensive functional changes in the PVN and RVLM [61,62]. Such central effect of circulating AngII involves its action on CVOs including SFO area postrema (AP), which promotes sympathoexcitation from RVLM *via* PVN and NTS [41,46]. In addition, brain AngII, as part of brain RAAS, was shown to substantially increase BP in animal hypertensive models. To understand this, intracerebroventricular infusion of AngII was carried out and found to heighten BP and cardiac sympathetic outflow by inducing a pro-hypertensive activity in the PVN [30,43]. Moreover, Su et al. showed that, in response salt intake, brain AngII promotes sympathoexcitation in the PVN by increasing ROS production in the PVN [63]. In the central nervous system, AngII stimulates not only neurons [46] but also innate immune system to induce hypertension [61]. In their investigation, Mowry et al. showed that AngII promotes sympathoexcitation in the PVN and RVLM of SHR by binding to AT1R which crosstalk with Toll-like receptor 4 (TLR4) on the microglia. Moreover, AngII infused subcutaneously increased both the microglial cell number and their activation and the proinflammatory cytokines (PICs) mRNA transcription in the PVN and this effect was associated with elevated plasma level of NE and BP [64]. Activation of these immune residents and neural activation maintain neurogenic source of hypertension [65]. Other mechanisms of AngII in sympathoexcitation through the PVN involve the activation of Hypoxia-Inducible Factor-1α-*N*-methyl-D-aspartate receptor [43] and crosstalk between angiotensin receptor AT1R and α1-adrenergic receptors [66]. Hence, in addition to the peripheral effect of the crosstalk between AT1R and α1-adrenergic receptors on cardiomyocytes [67] and smooth muscle cells [68] resulting in mutual potentiating effects of both receptors, central interaction between both receptors activation has been reported in rat brain [69]. AngII, through AT1R, was shown to increase the expression of norepinephrine transporter in rat neurons [70] and hence to promote de release of this neurohormone, which in turn reduces the expression of AT1R. This depicts an important crosstalk whose lack may favor hypertension as observed in SHR [69]. In summary, both peripheral and central AngII induce hypertension through neuroexcitation and neuroinflammatory activity in cardiovascular regulating centers [61,71,72].

Table 1
Bioactive soluble factors reported to enhance sympathetically – driven hypertension in animals through central action.

No	Bioactive factors	Route of infusion (source)	Investigated brain region	References
1	AngII	Intravenous (peripheral), intra-PVN (central), subcutanous (peripheral), intracerebroventricular (central)	Subfornical organ (SFO), PVN, NTS	[16,30,40–47]
2	Aldosterone	Subcutanous (peripheral)	SFO	[48]
3	(Pro)renin	Central	PVN	[49]
4	TNF-α	Intravenous (peripheral), intracarotid artery (peripheral), intra-AP (central)	PVN; RVLM, AP	[16,26,29,50]
5	Interleukin-1beta (IL-1β)	Intravenous (peripheral)	SFO, PVN	[26,51]
	LPS	Intraperitoneal (peripheral)	NTS, PVN	[52,53]

3.2. Aldosterone

Another component of RAAS reported to influence the progression of hypertension through central effect is aldosterone, the principal mineralocorticoid steroid hormone from the outermost layer of the adrenal gland. Compelling evidence from animal experiments data suggested the existence and the activity of brain aldosterone, which mediates hypertension. Huang et al., seeking to understand whether aldosterone mediates and amplify the central action of subcutaneously infused AngII, blocked the central synthesis of aldosterone. This reduced the production of aldosterone in the PVN without affecting its circulating level. Importantly, while the aldosterone synthase (AS) inhibitor attenuated AngII infusion – induced neuronal activity in the PVN, the neuromodulatory activity of AngII in SFO was not affected suggesting that brain aldosterone amplify the central effect of AngII [73]. Later, the same team demonstrated that circulating aldosterone would also have central effect through the SFO where this hormone induces a central aldosterone synthesis [48] and mediates the action of AngII in ROS production [74]. This mediative role of brain aldosterone to both circulating and central AngII-induced hypertension is also supported by previous findings in which the inhibition of peripheral aldosterone synthesis with the molecule FAD286 did not influence the pressor effect of AngII while that of central aldosterone synthesis with the same molecule did [45]. Taken together, these findings support the central effect of aldosterone as a peripherally released soluble factor.

3.3. (Pro) renin and its receptor (P)RR

As an essential enzyme in the production of AngII, (pro) renin is a kidney originating protein and an important component of RAAS. Therefore, its role in the regulation of BP through its receptor is well accepted [75,76] and inhibition of their interaction is of therapeutic importance [77]. To induce its catalytic effect, (pro) renin binds to its receptor (P)RR unmasking its catalytic site, which leads to the enzymatic activity of the protein [78]. In circulating, both (pro) renin and (P)RR co-exist as soluble factors, which explain the enzymatic activity of (pro) renin producing AngI, which is converted to AngII [79]. Despite its late discovery, the brain (P)RR, gained attention and has been implicated in the brain mechanism of controlling cardiovascular function [80]. Beside its soluble form [79], neural cells have been shown to express (P)RR [81] supporting the implication of brain RAAS along with the peripheral system in controlling BP [82]. Whether brain renin is locally synthetized or is of circulation origin remains less explored. However, in their study, Thiel et al., demonstrated that (pro)renin found in the brain of mice was of circulating origin and that there was no (pro)renin synthesis in the brain [83]. The role of (P)RR in mediating hypertension, in contrast, gained attention. Li et al., showed that brain (P)RR mediated AngII-induced hypertension as knocking down (P)RR prevented the

progression of hypertension in human renin-angiotensinogen transgenic mice [84]. In addition, while deoxycorticosterone acetate (DOCA) and AngII-induced hypertension in mice was not associated with change in brain (pro) renin level [83], Li et al., found that, (pro) renin or DOCA-induced hypertension was mediated by central (P)RR. However, they did not investigate the (pro) renin level [77]. Moreover, brain cardiovascular regulating centers, namely PVN, NTS and RVLM and the SFO were found to express this receptor [49,77,81,84]. Finding of the expression of (P)RR in CVOs such as SFO, without cardiovascular relevance [81,84], support previous conclusion that brain (pro) renin that may activate (P)RR is soluble bioactive factor with central effect [83].

3.4. Tumor necrosis factor alpha (TNF-α)

TNF-α is a cytokine with well-documented role in the modulation of BP and consequently its implication in the pathogenesis and pathophysiology of hypertension. Although its link with chronic diseases was accepted for long time long [85], TNF-α, as an important component of the progression of hypertension in human, was reportedly suggested in late 90s of the last century [86] and found to be higher in both serum and 24-hour urine in hypertensive patients than in those of normotensive people [87]. Investigations in animal models including mice and rats argue for the strong implication or mediation of TNF-α in hypertension [85]. Thus, TNF-α was not only elevated in different experimental hypertensive models but importantly, its specific inhibition improves hypertensive condition [86,88–90].

The sympathetically mediated hypertension depicts how much capital role does the nervous system play in hypertension. Signaling molecules promoting increased sympathetic drive include TNF-α, which is produced both in circulation and within the central nervous system. The central effect of TNF-α on the progression of hypertension was shown in animal models, which develop hypertension in response to intracerebroventicular [51], intravenous and intracarotid artery [50] infusion of this cytokine. In the cardiovascular regulating centers such as the PVN or in the SFO, TNF-α binds to its type 1 receptor, TNFR1, to promote neuroexcitation [51], neuroinflammation and oxidative stress [26,90]. Similar to other bioactive factors, both peripheral and centrally produced TNF-α affect the sympathetic preganglionic neuronal circuits, emanating from AP [91], SFO [26,92,93], in the PVN [26,94] leading to increased sympathoexcitation toward kidney, heart and blood vessels [29]. Peripheral and central infusion of TNF-α increases BP in rat [26,94] by acting on neurons to induce direct effect or collaboratively. Using patch-clamp techniques, Simpson and Ferguson showed that TNF-α increases the neurons excitability in the SFO in rat [93]. In addition, TNF-α is known to potentiate the effect of AngII in the brain. Thus, in their experiment, the team of Joseph showed that restoration, by infusion, of TNF-α improved the blunted response to AngII infusion in TNF-α knockout (TNF-α−/−) mice [95]. Moreover, in an *in vitro* experiment using neuron from the SFO, it was shown that TNF-α potentiate the effect of AngII in intracellular Ca^{2+} induction [92]. Importantly, TNF-α infusion in the SFO upregulated the mRNA of angiotensin converting enzyme (ACE) and AT1R, two components of RAAS in the SFO and the PVN as well as TNF-α, IL-1β and their receptors [96]. Similar findings were obtained in rat infused with TNF-α *via* intracarotid artery [97]. More importantly, AngII could stimulate the production of TNF-α and IL-1β in neuronal culture [98] suggesting a reciprocal effect of TNF-α and AngII on their bioactivity. Collectively, these findings suggest an interplay between of TNF-α and AngII and a synergic action of TNF-α and AngII on their receptors to promote sympathoexcitation initiated from CVOs and cardiovascular regulating centers.

Both neurons and neuroglia express TNFR1 whose activation promotes neuronal hyperexcitability in spinal cord in response to TNF-α [99], in the PVN in response to AngII infusion [42] and in the AP of renovascular hypertensive animals [29]. In cardiovascular regulating centers, the molecular mechanism of TNF-α-TNFR1 signaling may involve epidermal growth factor receptor (EGFR) and Extracellular signal-regulated kinase 1/2 (ERK1/2) signaling in the both SFO and PVN [97]. Activation of this receptor by TNF-α also contributes to *N*-methyl-D-aspartate (NMDA) receptor activation-induced excitation in PVN neurons in mice in response to AngII infusion [42]. *In vivo* experimental studies, the precise molecular mechanism by which TNF-α induces is not fully delineated. However, increased production pro-inflammatory factors and RAAS components in SFO and PVN have been reported in rat in response to TNF-α infusion [26,51,96]. In SHR, central inhibition of TNF-α in the PVN with pentoxifylline or Etanercept, preventing TNF-α to bind to its receptor, attenuated the production of PICs and ROS supporting the contribution of TNF-α signaling in the PVN to the progression of hypertension in this model [90]. Importantly, the activation of NF-κB has been associated with the complex TNF-α-TNFR1 [100] and the NF-κB inhibition within the PVN attenuated the sympathoexcitation-induced hypertension in SHR [101].

3.5. Interleukin-1beta (IL 1β)

IL-1β is a proinflammatory cytokine produced in response microbial infection or tissue injury. Extensive reviews focused on the mechanism of production and release of IL-1β and reported that the production of IL-1β does not use the classical protein production path *via* endoplasmic reticulum-Golgi route. In addition, the release of IL-1β involves different modalities including exocytosis of secretory lysosomes, macrovesicles shedding from the plasma membrane, exosomes, across the plasma membrane [102,103]. Produced by monocytes, macrophages and dendritic cells in form of pro-IL-1β, this cytokine becomes active upon the proteolytic action of caspase-1 and has broad biological activity including increasing tumor invasiveness, tissue damage [103], obesity-induced insulin resistance [104] and promotion of cardiovascular diseases [51]. As one of the early-response cytokines [105], IL-1β induced the production of other cytokines such as IL-6, IL-17, IL-23 [106] which contribute to the chronicity of inflammation in some pathologies.

Hypertension is a state of low grade and chronic inflammation, which plays important role in the onset as well as the progression of the disease. In hypertensive patients and animal models, this state is materialized by increased proinflammatory soluble factors including IL-1β in both circulation and within tissue/organ [105]. Similar to TNF-α, IL-1β is increasingly implicated in the progression of hypertension through its effect on vessels and on kidney where it promotes ROS production, endothelial dysfunction, vasoconstriction [105,107] and on central nervous system where it promotes sympathoexcitation [51,108]. In their experiment, the team of Zhu showed that capsaicin-induced excitatory renal reflex, marked by increased MAP and renal sympathetic nerve activity (RSNA), could be blunted by both the inhibition of the production of IL-1β and the antagonism of IL-1β receptor using IL-1β receptor antagonist (IL-1Ra) in the PVN. Such inhibition demonstrated that capsaicin-induced excitatory renal reflex requires IL-1β expression and activity in the PVN and involves the synergic activity of RAAS component as evidenced by the reduction in IL-1β expression in the PVN in response to captopril and losartan microinjection [108]. Other investigations showed that increased IL-1β expression in the PVN promotes hypertension through sympathoexcitation [51,96]. Importantly, like previously described soluble factors, circulating IL-1β own a pro-hypertensive effect by acting on the SFO through its type 1 receptor (IL1R1). This was materialized by the increased sympathoexcitation and BP in rat in response to intravenous injection of IL-1 β [26,51,96]. Moreover, the therapeutic potential of this cytokine was suggested in hypertension [105].

3.6. Lipopolysaccharide (LPS)

As an innate immune response stimulus, LPS, produced by gram-negative bacteria, is used to develop peripheral inflammation in animal models. The link between LPS and hypertension may reside in not only peripheral inflammation but also neuroinflammation induced by

LPS. Several studies demonstrated the ability of LPS to promoting endothelial dysfunction and vascular inflammation, which may contribute to peripheral resistance and potentially hypertension as reviewed elsewhere [109]. These effects of LPS involve the activation of TLR4, the production of PICs, the activation of nuclear factor-kappa B (NF-κB), the overproduction of ROS and other proinflammatory and oxidative products [109]. Importantly, one of the early central effects of LPS is neuroinflammation marked by increased production of PICs in response to the activation, by LPS, of microglia, astrocytes and perivascular macrophages closer to blood-brain barrier (BBB). *In vitro* study on neural cells showed that LPS can directly activate N9 cells (microglia cell line) and induce the production of PICs by this cell line [110] and can also stimulate neuronal cells as evidenced by the study using NE-4C cells, a murine neuronal cell line, which reported that LPS mediated inflammatory effect on neuronal cells [111]. *In vivo* studies reported the neuroinflammatory effect of LPS. In C57BL/6 J mice, intraperitoneal injection of 5 mg/kg of LPS resulted in increased expression of PICs and microglial activation marker, the Ionized calcium binding adaptor molecule 1 (Iba1), in the brain [112]. In another study, 5 μg LPS was infused in the brain through intracerebroventricular injection. This procedure resulted in neuroinflammation [110]. Both peripheral and central administration of LPS promoted neuroinflammation and induced cognitive impairment in mice [113]. Of different regions affected by LPS-induced neuroinflammation, the PVN was reported to respond to LPS signal and display a pro-hypertensive activity. Thus, intraperitoneal injection of 5 mg/kg of LPS to Sprague Dawley rat induced a typical neuroinflammatory response followed by and increased neuro-excitation rate in the PVN. This neuro-excitation was directed to the RVLM, as proved by the increase in firing rate of PVN-RVLM neurons in this model [114]. Importantly, such brain activity, in response to LPS promoted the overactivation of the sympathetic system, which was marked by increased circulating NE level. This finding supports the idea of the role of LPS in hypertension. Earlier, Wu et al., showed that two weeks chronic intraperitoneal infusion of 1.2 mg/kg/day of LPS induced not only neuroinflammation in the RVLM but also elevated BP [25]. Taken together, these findings demonstrate the potential of LPS in promoting hypertension *via* its central effect on cardiovascular centers including the PVN where it promotes autonomic dysfunction [115].

LPS is recognized by the membrane receptor, the Toll-like receptor 4 (TLR4), on innate immune cells or other cells expressing such receptor and blockade of TLR4 prevented the detrimental effect of LPS. Binding of LPS to TLR4 activates the myeloid differentiation primary response gene 88 (MyD88)-dependent pathway inducing PICs expression and the MyD88-independent (TRIF-dependent) pathway leading to the expression of type I interferon [116]. MyD88-dependent pathway promotes the production of PICs, mainly TNF-α and IL-1β through the phosphorylation and nuclear translocation of the nuclear factor-kappa B (NF- κB) [117]. Activation of this pathway is involved in several cardiovascular diseases including hypertension [118–121]. A TLR4-specific inhibitory peptide, VIPER, was shown to blunt the LPS-induced neuroinflammation and cognitive impairment, effect that involves the activation of NF-κB signaling pathway [113]. In the PVN, VIPER also attenuated LPS-induced neuroinflammation, microglial activation and autonomic dysfunction [115] demonstrating the importance of TLR4 activation in this effect. Thus, conditions promoting the activation of TLR4 in the PVN may also induce the sympathoexcitation emanating from this center. Thus, Wang et al., showed that knocking down TLR4 in the PVN prevented myocardial infarction-induced sympathetic hyperactivity similar to that induced by LPS [122]. Importantly, both *in vitro* and *in vivo* experiments concluded that the LPS-TLR4 complex activation implicates the NF-κB/PICs signaling to alter cardiovascular function [109,113,122,123].

4. Central targets of peripheral factors in hypertensive models

To decipher how circulating factors contribute to the neurally mediated hypertension, brain anatomical structures, targets of those factors, have been investigated. Although in previous sections of this review, those structures have been mentioned, summarizing evidence regarding their contributions to the neurogenic aspect of hypertension may be helpful at this stage. It is well demonstrated that most circulating factors implicated in the neurally mediated hypertensive development are large to cross the physical barrier represented by the BBB. This makes the CVOs, potential relays of peripheral factors to central structures [17,18]. The CVOs – cardiovascular regulating centers – peripheral organs axis becomes an important path of investigation in the field of hypertension. Of the CVOs, SFO, organum vasculosum of lamina terminalis (OVLT) and AP, which are "sensory CVOs", have been explored for their mediative role in hypertension. The Fig. 1 depicts the most commonly investigated components of the aforementioned axis which will be detailed the following sections.

4.1. Circumventricular organs (CVOs)

4.1.1. Receptors for circulating factors in the SFO

Peripheral soluble factors induce their effect on target cells/tissues trough their receptors, which are mostly constitutively expressed. Number of animal experiments reported the expression of receptors for different pro-hypertensive factors in the SFO. Thus, the expression of AT1R, the pro-hypertensive signal receptor for AngII and that of the receptor of aldosterone (mineralocorticoid receptor, MR) were detected in the SFO in response to subcutaneous infusion of AngII or aldosterone [48,74,124,125]. These studies demonstrated the (elevated) expression of MR in the SFO where this receptor is the target of peripheral aldosterone leading to the generation of ROS and enhanced AT1R activity and eventually the central production of aldosterone that could affect the PVN activity [48,74]. Such conclusion corroborates earlier findings reporting that systemic blockade of MR with orally administered eplerenone attenuated the neural excitation and PICs production in the PVN. Increase in the expression of these receptors in the SFO was associated with heightening in BP with subsequent pro-hypertensive activity of the PVN [48] and RVLM [124]. The SFO expresses the receptor of another RAAS component that may contribute to the pro-hypertensive activity of this structure. (Pro)renin receptor (P)RR was shown to be expressed in the SFO where it contributes to local RAAS activity [81,84]. In addition to the receptors of RAAS component, the SFO mediates the effect of circulating inflammatory factors by expressing their receptors. To demonstrate this, peripheral infusion of either TNF-α or IL-1β in rat was carried out. These PICs increased BP by acting on their receptors located within the SFO. Such infusion increased the expression TNFR1, IL1R1 and ATR1 in the SFO [26,51,96]. Recent evidence from the same team elucidated a *de novo* proinflammatory factors expression within the SFO in response to peripheral TNF-α infusion. The mechanism includes activation of EGFR and ERK1/2 signaling involving NF-κB, the PICs transcription factor, in the SFO [97].

4.1.2. Receptors for circulating factors in the OVLT

OVLT is another sensory CVOs with hypertensive relevance. Experimental data showed the potential of OVLT in mediating hypertension in rat [126,127]. Thus, lesion at the OVLT attenuated DOCA [127] or AngII-induced hypertension in SD rat [128,129]. Evidence for the expression of the receptor for AngII was not provided by either study. However, the expression of AT1R in mouse OVLT without linking such expression to hypertension has been provided [72,125]. Although expressed, the mRNA level of (P)RR was not different in OVLT from SHR compared to that from Wistar Kyoto (WKY) rats suggesting that this CVO mediates less the activity of (pro)renin in their sympathoexcitatory effect [80]. Despite reported to mediate neuroimmune communication, direct evidences of peripheral immune factor activation of OVLT with cardiovascular relevance are sparse [130].

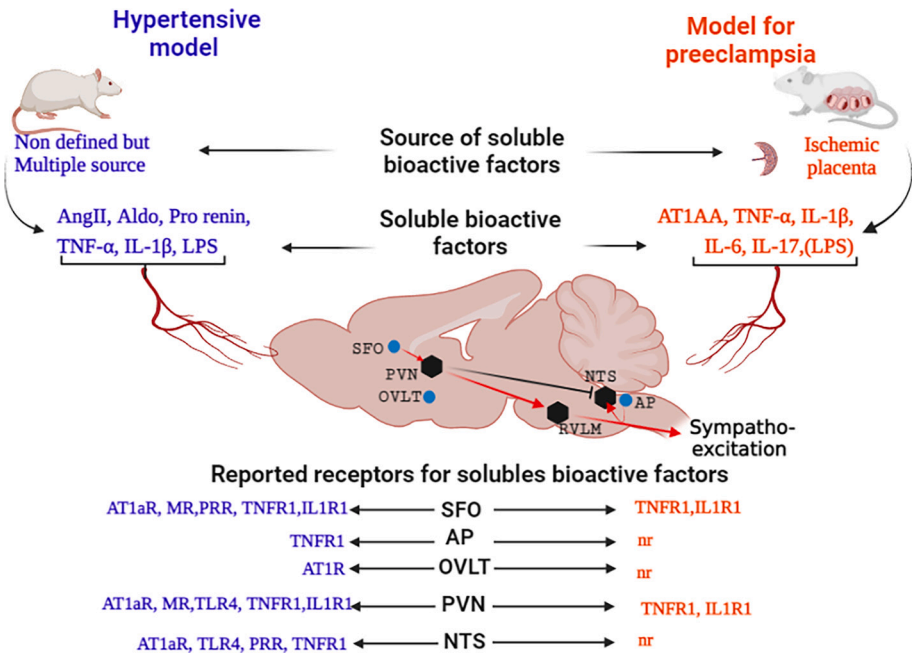


Fig. 1. Summary of comparative findings suggesting the existence of neural mechanisms of hypertension in preeclampsia.
Different blood-borne soluble factors of different sources act on brain regions with relevance to cardiovascular function to promote rise in sympathoexcitation and blood pressure. This is possible *via* their molecular receptors expressed on neural cell (neurons, microglia) in different regions. PVN: paraventricular nucleus of hypothalamus; SFO: Subfornical organ; NTS: Nucleus of solitary tractus; RVLM: rostro-ventrolateral medullar region; AngII: Angiotensin II; Intra-AP: intra- area postrema; TNF-α: Tumor necrosis factor-alpha; TNFR1: TNF-α type 1 receptor; IL-1β: Interleukin-1 beta; IL1R: IL-1β type 1 receptor; LPS: Lipopolysaccharide; Ang: AngiotensinII; AT1R: AngII type 1 receptor; AT1AA: AT1Auto Antibody; TLR4: Toll-like receptor 4; MR: mineralocorticoid receptor; (P)RR: (Pro) renin receptor; nr: Not reported; OVLT: organum vasculosum of lamina terminalis.

4.1.3. *Receptors for circulating factors in the area postrema*

The AP, important for autonomic regulation, has direct link to the NTS and RVLM and modulates the sympathoexcitatory output in hypertension. A recent investigation showed that this CVO contains neurons expressing receptors for PICs, particularly the TNFR1 [91]. The authors showed that activation of such receptor by TNF-α fires neurons and promotes sympathoexcitation toward RVLM as evidenced by the findings of retrograde labeling performed in their study [91]. In addition to the action of circulating and cerebro-spinal fluid (CSF) cytokines, several factors/condition including AngII, DOCA and obesity activate microglia in this region leading to increased production of TNF-α which would promote hypertension [131]. Together, these reported suggest that AP in a potential target for circulating factors with cardiovascular regulation relevance.

4.2. *Cardiovascular regulating centers*

Midbrain and brain stem cardiovascular regulating centers are integrating centers receiving inputs from other regions including but not exclusively the CVOs. Through neurohormonal connections, these centers modulate the cardiovascular function in health and disease. In this review, we will focus on the PVN and the NTS, as centers with direct projections from CVOs and to the RVLM, source of sympathoexcitatoty outflow [132,133]. Changes occurring in cardiovascular regulating centers in relation to peripheral factors and hypertension will be discussed.

4.2.1. *Receptors for circulating factors in the PVN*

Both the PVN and the NTS lie behind the BBB and basically respond to peripheral signals through the mediation of CVO namely SFO and OVLT for the PVN and AP for the NTS [134]. However, in pathological condition, the disruption or increased BBB permeability may occur facilitating the surge of number of peripheral molecules to these regions. Thus, despite the sparsity of evidence regarding the status of BBB in hypertension, *in vivo* experiments reported the disruption of BBB in SHR model. Authors linked such disruption with AngII as both peripheral and central blockade of AT1R reduced the hypertension and prevented BBB disruption in the PVN and NTS in these animals [33,135]. Number of receptors for different peripheral signaling molecules is expressed in those regions protected by the BBB. In the renovascular hypertensive rat model, developed through two-kidney, one-clip (2K1C) method, the expression of the AT1R was upregulated as compared to sham [136]. Similar findings were reported from SHR [137]. In another hypertensive model, specific blockade of AT1R within the PVN prevented high salt (8 % in drinking water)-induced sympathoexcitation and hypertension recalling the important role of the activation of this receptor in hypertension [63,135]. In this way, not only centrally produced AngII will activate its receptor AT1R in the PVN but also the peripheral AngII does so [44] through breaking the BBB [135] although the patterns of AngII-induced hypertension may differ between central and peripheral AngII [45]. Microglial [62] and neuronal AT1R is the target of this molecule in the PVN, where, the downstream effect of the activation of AT1R includes ROS production [63], neuroinflammation [72], factors known to promote sympathoexcitation from the PVN.

Compelling evidence support the role played by the MR in the PVN for neurogenic hypertension in response to AngII or aldosterone infusion [16]. Blockade of MR with eplerenone in the PVN attenuated the pressor response of centrally administered AngII including rise in BP [44,45]. Importantly, knocking down MR in the PVN through siRNA method did not only downregulate the expression of MR but also that of AT1R. Conversely, knocking down AT1R only downregulated the expression of AT1R suggesting that in the PVN, MR mediates and enhances the activity of AT1R [48,138]. Moreover, central MR promotes sympathoexcitation potentially through heightening of PICs and ROS generation in the PVN [139,140].

The PVN is also the site of expression of receptors for proinflammatory factors. Activation of these receptors was associated with sympathoexcitation. In a recent study, Woods et al. showed that knocking out TNFR1 through short hairpin RNA (shRNA) method in the PVN attenuated AngII-induced hypertension. In addition, this TNFR1 was shown to be expressed on neurons promoting sympathoexcitation [141]. Although constitutively expressed in the PVN, receptors for inflammatory factors are highly induced by stimuli in hypertensive condition. Wei et al., showed this through intracarotid injection of IL-1β, which upregulated the TNFR1 and IL1R1 in the PVN and was associated with sympathoexcitation and elevated BP [51,96]. The TLR4, known to be activated by LPS was shown to promote hypertensive phenotype in mice as its knocking out within the PVN blunted the sympathoexcitation emanating from the PVN in response to LPS injection [122]. Moreover, this receptor was upregulated in the PVN of SD rat in response to LPS

injection and it's inhibition with VIPER reverted changes at molecular and cellular level and improved the autonomic dysfunction induced by LPS [53]. These findings reinforce the idea of interactions between inflammatory, RAAS [142] and oxidative stress components in the PVN to promote hypertension [63].

4.2.2. Receptors for circulating factors in the NTS

In addition to receiving input signal from baroreceptor afferent nerve fibers for the modulation of BP in normal range, NTS is also influenced by inputs from AP, a CVO, and from forebrain cardiovascular regulating centers, especially the PVN [134,143]. In response to increase in BP, barosensitive receptors are stretched and activated, increasing the firing rate of afferent neurons to NTS and leading to reduction in the sympathetic output from the RVLM *via* the inhibitory projection of caudal ventrolateral medulla [132]. However, neuronal projection emanating from NTS to RVLM is not only influenced by neurotransmitters. Number of molecules, part of RAAS or inflammatory process, has their receptors located on neural tissue within NTS. Activation of such receptors has been shown to play significant role in the progression of hypertension.

Receptors for AngII are found in NTS both in normal and hypertensive conditions. Using genetic engineering tools, Sumners et al., showed that both AT1aR and AT2R are constitutively expressed in the NTS [125], a structure implicated in the control of baroreflex, in mice suggesting the potential role of NTS AngII-AT1R signaling in hypertension [72]. Causing sympathoexcitation, by potentiating gamma-aminobutyric acid B $(GABA)_B$ receptors activation [144], and neuroinflammation are downstream effects of the activation of AT1aR in the NTS where this receptor promotes the production of PICs by interplaying with other pro-hypertensive receptors such as TLR4 [135]. Although its expression on other cell types than neurons is debated [125,145], AT1R activation in the NTS is associated with neural control of cardiovascular function. Mowri et al. showed that the expression of AT1R was higher in NTS from hypertensive model, the SHR, than that from normotensive rats, the WKY rat. More importantly, blocking this receptor inhibited the expression of neuroinflammatory factors including PICs and microglial activation as well as elevation in BP [135]. Another receptor, part of RAAS extensively reported in the NTS relatively to cardiovascular regulation is the (P)RR. Although expressed in less extent in NTS than in other cardiovascular regulating centers, (P)RR is reportedly present in the brain [84]. A previous study showed that (P)RR expression was higher in NTS of SHR than in that of WKY rats. In the same study, *in vitro* assay showed that neuronal culture from SHR produced more mRNA for (P)RR than did that from WKY rat. While it showed pro-hypertensive effect of (P)RR, as demonstrated by knockdown of (P)RR, in SON, this study did assess the effect of this receptor in the NTS on hypertension in this model [80]. Later, Zubcevic et al., concluded on the antihypertensive effect of (P)RR within the NTS in SHR. Indeed, knocking down (P)RR in the SHR through sh-RNA increased the MAP while its stimulation by infusing renin attenuated the elevation in MAP [146]. Contrary to the association of pro-hypertensive activity with neuroinflammation, these authors found that chronic knockdown of (P)RR while increasing BP significantly reduced the expression of neuroinflammatory factors including NF-κB. This *in vivo* finding was supported by *in vitro* assay showing that activation of (P)RR by (pro)renin increased inflammatory factors in neuronal cell culture [146].

NTS also expresses receptors for inflammatory factors. In two different models, the expression level of TNFR1 was elevated. This increased expression was associated with elevated BP in SHR [147] and 2K1C rat [91] models. This receptor was localized on neurons from NTS projecting to the RVLM [91] suggesting the contribution of TNFR1 to the neuro-modulation of cardiovascular function by the NTS. Moreover, TNFR1 being activated by PICs, namely TNF-α implies that neuroinflammation in the NTS may promote neurogenic component of hypertension. In line with this idea, Fu et al., showed that peripheral infusion of LPS triggered systemic inflammation as well as increased neuroinflammation within the NTS marked by increased PICs expression and microglial activation [52]. To act, LPS is recognized by the TLR4, which becomes activated and promotes the release of PICs. Such receptor was elevated in NTS of SHR and its blockade attenuated the expression of PICs, microglial activation and increased BP demonstrating the pro-hypertensive role of TLR4 in the NTS [135].

5. Potential for placental derived pro-hypertensive factors (PDHF) in mediating autonomic dysfunction in PE

5.1. Placental derived pro-hypertensive factors

As one of most obstetrical complication, PE is an important concern for health care system due to its complication for mother and fetus. Epidemiological studies reported that PE increases the risk for mother and fetus to future cardiovascular diseases [148]. Despite that described earlier in textbooks, PE remains enigmatic, as its exact etiology remains unknown. However, decades of intensive investigations revealed the fundamental role played by the placenta in the onset and progression of this condition since fetal delivery alone is not sufficient for the remission of the condition but requires placental removal [149,150]. Clinical findings support the idea that placental maladaptation/dysfunction during pregnancy constitutes the causative event to placental hypoperfusion causing ischemic environment within this organ. Such placental ischemic state triggers the release of number of soluble bioactive factors, the placental derived pro-hypertensive factors (PDHFs), responsible for vascular dysfunction and hence hypertension in PE [21,151]. Animal models mimicking PE condition as well as *in vitro* assays on placental-derived material with hypoxic condition release a variety of soluble factors in circulation or culture media [21]. Although their identity is still not fully delineated, the PDHFs including angiogenic factors, immune factors, and other vasoactive factors such as nitric oxide (NO) and endothelin have been reported in PE [152]. The common feature of all these factors being their ability to alter endothelial function resulting in hypertension [151].

Angiogenic factors shown to be involved in PE include anti-angiogenic factors, mainly the soluble fms-like tyrosine kinase 1 (s-Flt1) and the soluble endoglin (sEng), elevated in PE women and animal models [153,154], which blunt the effect of the second subgroup, the pro-angiogenic factors. The latter mainly include the vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and transforming growth factor (TGF)-β1 whose circulating level is reduced in PE patients and animal models [152]. Importantly, in addition to its potential as biomarker for PE, animal experiments revealed that infusion of s-Flt1 induced PE like symptoms in rat [155] and mice [154] supporting its causative role to the maternal phenotype. The effect of increased circulating s-Flt1 and sEng is mainly to reduce the bioavailability of circulating VEGF and TGF-β1, respectively, hence their bioactivity, rather than inducing any signaling pathway in this placenta and blood vessels. This, ultimately reduces the cellular signaling of these two pro-angiogenic factors and subsequently impairing the vasodilation [152].

As a condition with imbalanced immune response, PE is characterized by increased pro-inflammatory factors and diminished anti-inflammatory or immune-regulatory factors. Both cells and soluble factors, especially cytokines, which promote excessive inflammation are elevated in patients and animal models for PE [156]. Of the PICs, TNF-α, IL-6 and IL-17 are elevated in PE and are thought to play a mediative role to the maternal condition. To confirm these observations, the placental or circulating levels of these cytokines were evaluated in reduced uterine perfusion pressure (RUPP) rat, a model mimicking placental ischemia. Different research groups found that placental insult increased placental expression [157,158] or circulating level [159–161] of TNF-α in RUPP rats. Both placental and circulating levels of IL-17 were also elevated in RUPP rats [158]. Moreover, infusion and specific inhibition of these cytokines respectively induced and improved PE-like symptoms. Thus, infusion of TNF-α [161,162], IL-6 [163] or IL-

17 [164] resulted in PE-like symptom in rat with increased MAP, increased placental and circulating inflammatory factors supporting the role of excessive inflammation in PE as well as the direct effect of these PICs in the onset of maternal hypertension in PE. Importantly, specific inhibition of TNF-α with Etanercept, its soluble receptor [165] or that of IL-17 with its soluble receptor, the IL-17RC [158] improved maternal condition in RUPP rat. As stated earlier, the overall effect of these cytokines is to promote endothelial dysfunction in PE.

As the most active peptide in RAAS, AngII level was evaluated in both normotensive pregnants and PE. Results revealed that circulating AngII level did not differ from both states [166]. However, compared to non-pregnant state, pregnant women reportedly had higher circulating AngII level and PE women have reduced level compared to normotensive pregnants [167]. Despite significant change in some placental RAAS components in PE [168] including increased sensitivity to AngII, which may pave the road for the onset of hypertension [169] there is a lack of direct evidence of changes in RAAS components-induced PE like symptoms. However, although not specific to PE, the presence of autoantibodies against AngII type 1 receptor (AT1AA) in PE women was reported in several clinical studies [170]. Importantly, these antibodies were not only elevated in animal models for PE including the RUPP, but their ability to induce PE-like symptom was evidenced [171]. Thus, infusion of AT1AA to normal pregnant rats increased AT1AA level and elevated BP as well as other symptoms [171,172]. Although AT1AA targets AT1R, these antibodies do not compete with AngII but potentiate the effect of AngII instead. Thus, co-administration of AngII with AT1AA promotes pro-hypertensive phenotype of the kidney as compared not only to control but also to the infusion of AngII or AT1AA alone [173]. The pro-hypertensive activity of AT1AA in PE involve the production of TNF-α [174], stimulation of endothelin signaling pathway [172,175], increased ROS production [175], stimulation of the production of two powerful antiangiogenic factor namely sFLT and sEng [176]. All these factors are well known to promote hypertension through their effect on kidney and blood vessels.

Placenta express RAAS components including the (P)RR, angiotensinogen and AT1R, which were shown to be elevated in placenta from PE, may be induced by low oxygenation. This was shown *in vitro* study when placental explant expression of mRNA for angiotensinogen AT1R increased in response to oxidative stress induced by alternating hypoxia–re-oxygenation period over 24 h [177]. Angiotensinogen being the substrate of the complex (P)RR-renin, placental ischemia may initiate the activation of placental RAAS components. To understand the association between placental and circulating (P)RR and BP in pregnancy, Narita et al., found that level of (P)RR in both media were not only elevated in PE, as compared to normotensive pregnant women, but also positively correlated with the BP level and may affect renal functions [178]. Importantly, data from other teams confirm this increased (P)RR level in PE and in DOCA–induced PE model in rat [179,180]. Whether placental ischemia induced in RUPP would increase (P)RR level has yet to be studied. Interestingly, a recent study showed that increasing the expression of circulating and placental RAAS components in rat, using transgenic rats, increased BP similar to that in RUPP. More importantly, silencing the expression of angiotensinogen, using Small Interfering RNA (siRNA), significantly reduced hepatic but not placental level of this hormone, this in both transgenic and RUPP rat model [181] suggesting less contributory role of placental angiotensinogen to PE – like symptoms.

5.2. Potential for PDHF in autonomic dysfunction in PE

A number of bioactive factors have been reported to link placental ischemia to the maternal hypertension in PE. To date, it is believed that these bioactive factors promote hypertension through general endothelial dysfunction and pressor effects [182]. The molecular mechanisms of most of these factors in PE have been extensively reviewed by others and mainly concern the peripheral pressor effect of these agents and lie out of the scope of this review [156,182,183]. As presented in previous sections, the role of several of these factors in the progression of human primary or secondary hypertension is well documented. Hypertension in PE is a secondary hypertension as it stops with the delivery or placental removal. Yet, whether there is a neurogenic component of the hypertension in PE is not clear. This raises interesting in knowing whether PDHFs would contribute to the neurogenic component of hypertension in PE.

Pregnancy is marked by early rise in muscle sympathetic activity, reduced sympathetic vascular transduction and lowered BP and vascular resistance [184]. Clinical and experimental data suggested the role of sex hormones, mainly estrogen, to contribute to such lowered vascular resistance through their effect on endothelial bed which involves nitric oxide (NO) [185]. In PE related hypertension, the altered neural control of BP [186], the increased SNA [187] and the autonomic imbalance [188,189] depict the potential neurally-mediated hypertension in PE. Although the mechanism is not elucidated, the role of placental derived factors has been suggested [186].

As one of the mechanisms of regulation of BP, the neural control of BP, which involves the baroreflex, is obviously impaired in PE along with other mechanism including renal regulation. Early finding of autonomic imbalance in PE supports the hypothesis of impaired neural control of BP in PE [186,190]. In pregnant women, the measurement of plasma norepinephrine (NE) as surrogate of sympathetic vasomotor activity (SVMA) is not efficient, due to several influencing factors including increase plasma volume, making the microneurography a credible alternative for SVMA. However, the invasiveness of this procedure limits its use to the late gestation [185]. In PE patients, VMSA is higher than that in normotensive pregnant women, which is also higher than that in non-pregnant women [190] suggesting that a "threshold in SVMA" should be reached before vascular transduction occurs and leads to elevation in BP. In PE women, changes that occur in autonomic regulation centers within the brain are still unknown. To understand mechanisms contributing to elevated SNA in normal pregnancy and exaggerated increase in SNA in PE, the group of Brooks conducted a study on the role the PVN in pregnant rat. After having confirmed that pregnancy in rat was associated with decreased MAP and elevated SNA, this team showed that increased excitation of neurons in the PVN by α-melanocyte–stimulating hormone and reduced tonic neuropeptide Y inhibition plays critical role in heightening SNA [191]. In RUPP rat, Spradley et al., showed that placental ischemia in rat was associated with impairment in adrenergic signaling and that blockage of adrenergic receptors, with Terazosin hydrochloride and propranolol hydrochloride, prevented RUPP-induced hypertension [192]. This study reinforced the conclusion of previous associative studies on the contribution of SNA and adrenergic receptors in vasoconstriction in PE [192,193]. In pregnant rat, Shi et al., showed that, although known for their sympathoexcitatory role, two soluble factors namely insulin and leptin, do not contribute to the increased SNA in pregnant rat [194]. This finding partially implies the need of identifying sympathoexcitatory soluble factors that may contribute to exaggerated increase in SNA in PE. In other words, the need is to identify what soluble factors contribute to sympathoexcitation in response to placental ischemia.

In the light of reported pro-hypertensive activities of the PDHFs in PE models, mainly assessed peripherally, and the above-described neural mechanisms of hypertension, it is logic to hypothesize that the PDHFs would have central effect as comparatively summarized by the Fig. 1. This is strengthened by two facts: findings of elevated level of many PDHFs in circulation on one hand and increased BBB permeability in PE models on the other [165], making several brain regions vulnerable to the surge of PDHFs. Direct evidence of molecular and cellular changes within brain regions with cardiovascular relevance in PE model are sparse. However, we previously found that placental ischemia increased MAP, circulating TNF-α and promoted a pro-hypertensive activity of the SFO and the PVN. Such activity was marked by increased production of PICs and their receptors, neuronal excitation and microglial activation.

Importantly, infusion of TNF-α to pregnant rats induced similar molecular and cellular changes in both PVN and SFO [161]. These findings clearly suggest the potential neuro-stimulating effect of TNF-α, as a soluble factor, in PE model. However, in that work, we did not measure the marker of SNA. To elucidate the mechanism of placental ischemia and infusion of TNF-α or any soluble factor demonstrated to induce PE-like symptom, further studies should block, in different cardiovascular-regulating centers, several signaling pathways to see whether such intervention improves the maternal phenotype in animals.

6. Conclusion

Hypertension is a multifactorial and chronic condition whose pathophysiology involves the neural mediation, especially in cases with resistant to many antihypertensive therapies. The neural role in this condition involves number of peripheral soluble factors that act on the CVOs, as gateways to cardiovascular regulating centers protected by the BBB. As secondary hypertensive condition, PE is marked by the increased circulating level of many of soluble factors demonstrated to promote rise in BP in animal model. Therefore, this review took the form of "hypothesis" supposing that the soluble factors in PE, termed placental derived pro-hypertensive factors (PDHFs) would promote the neurogenic components of hypertensive condition in PE in the light of the available data. The particular role of the PDHFs – CVOs – cardiovascular regulating centers – peripheral organs axis has been highlighted. Future studies would address this hypothesis to broaden our understanding of the pathophysiology of hypertension in PE.

CRediT authorship contribution statement

AIZ, ZW and ZM drafted the manuscript; AIZ, MMSO, XL, WXM, ZZS, YMK and JL edited and revised the manuscript; all authors approved final version of manuscript.

Funding

This work was supported by the National Natural Science Foundation of China NO. 82071670, 81771616 (Jinjun Liu).

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Data availability

No data was used for the research described in the article.

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