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Review on Circulating Endothelin 1 as a Pathogenic Relator for Endothelial Dysfunction in Preeclampsia

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KEYWORDS

Hypertension, Pathophysiology, Vasoactive, vasodilatation, vasoconstriction.

ABSTRACT:

In pregnancy, pre-eclampsia [PE] is a condition which is characterised by rise in systemic vascularity with proteinuria. It is considered as a major complication, known to cause considerable morbidity and mortality among pregnant woman and her offspring. Preeclampsia has remained elusive to the researchers with respect to its aetiology and pathophysiology. To acquiesce generation of the treatment to better management of PE patients, is too cognizant of search for molecular level key components which leads to pathogenesis of PE. Placental hypoxia is seen in PE, because of inadequate placentation leads, however, endothelial dysfunction is the basic mechanism which is setting the stage for the cascade of events ensuing in hypertensive disorders of pregnancy. Endothelin 1(ET1) is a marker of endothelial dysfunction and most prominent vasoactive member. Recent studies divulged that endothelin system as a pivotal path way for clinical manifestations of PE. To enlighten the role of ET1 as a marker of endothelial dysfunction and understanding the molecular mechanism underlying in pathophysiology of preeclampsia, the present review discusses on history, discovery, biosynthesis, mechanism of action and role of ET 1in PE.

Introduction:

This trend stress upon the fact that there needs to be stronger plan of action to identify, prevent and intervene into the factors causing maternal deaths. Disorders because of hypertension in pregnancy includes pregnancy-induced hypertension, preeclampsia, and eclampsia. 2% to 8% of pregnancy-related complications is associated with pre-eclampsia worldwide. This results in 9 to 26 percent of maternal deaths among low-income grouped countries and 16% in high-income grouped countries [1].

Pre-eclampsia can be defined as sudden development of high blood pressure, ≥140/90mmHg on 2 occasions which is 4 hours apart or more, with or without proteinuria or with significant end-organ dysfunction presenting after twenty weeks of gestation. [2 ,3]

Even after ample of research on exact cause for pathophysiology, the outcome is abstruse. Many theories

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have been put forth to explain the same. Theories of origin of preeclampsia are utero-placental, angiogenic, immunogenic and genetic predisposition [4,8]. However, the basic mechanism associated with preeclampsia is endothelial dysfunction [9].

The most recent and widely accepted is the two-stage model theory. This theory proposes that in the 1ststage, an inadequate trophoblast invasion causes deficient remodelling of spiral arteries leading to shallow placentation and poor utero-placental perfusion. As a consequence of events that occur in 1st stage, endothelial dysfunction and vascular inflammation sets-in resulting in clinical manifestation of the disorder, which is 2nd stage of the disorder with hypertension [10].

Endothelial dysfunction biomarkers are endothelium-derived vasoactive factors like circulating endothelin 1(ET1), Thromboxane A (TXA2), Angiotensin II are potent vasoconstrictors; and nitric oxide and prostacyclin are vasodilators. Flow mediated dilation (FMD) is considered as gold standard for evaluation of functionality of endothelium. Other markers like intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule 1(VCAM-1) and E-selectin can also determine its functionality. (11,13).

Moot pending question is what does engender the preeclamptic hypertension?

To enlighten the role of ET1 as a biomarker for endothelial dysfunction, which has been embroiled in contribution of hypertension and pathophysiology of preeclampsia, we conducted a literature review using database from PubMed and Google Scholar. The search terms we used were “Endothelin-1” [MeSH] and preeclampsia which was employed and able to identify the relevant studies published from 1990 to 2023. In this review. We have discussed the basic science of ET1, which includes History, Discovery, Biosynthesis, Mechanism of Action and Role of Endothelin1in Preeclampsia.

History and Discovery

In the culture media of bovine, the potent endothelium derived constricting factor was aortic endothelial cells which was found by circa in1985 and by Hickey et al. In 1988, Yanagisawa et al., ascertained the novel 21 amino acid vasoconstrictive peptide from porcine aortic endothelial cells which was cultured as endothelin (known as endothelin 1 or ET1) [14,15]. In 1989 Inoue et al., identified other two isoforms as ET2 and ET3 and completed the family of endogenous endothelin peptides [16,17]. The predominant endothelin peptide produced in endothelial cells is ET1. Each ET isoforms consists of 21 amino acid residues and expressed in various tissues. In 1990, Arai with colleagues and Sakurai with colleagues identified ETA and ETB novel transmembrane G protein coupled receptors [18,19, 20]. Takahashi et al in 1993 and Xu et al in 1994 identified Endothelin Converting Enzyme-1 (ECE-1) and while in 1995 they identified ECE-2[14]. Thus, the essential contents of ET pathway had been reveled [20]. Due to Endothelin sustained contraction properties, pharmaceutical industries discovered ET receptor antagonists [17].

Biosynthesis of Endothelin and Mechanism of Action

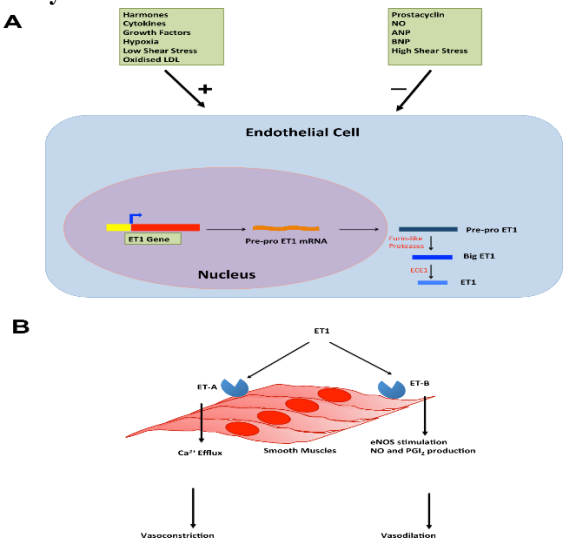

Figure 1: A-Diagrammatic representation of Endothelin 1(ET1) synthesis; B- its action.

ECE1: Endothelin Converting Enzyme1, ETA: G protein coupled ET A receptor and ETB: G protein coupled ET B receptor, eNOS: endothelial nitric oxide synthase, NO: Nitric Oxide, PGI2: Prostaglandin I2.

Endothelin 1(ET1) synthesis

ET1, ET2 and ET3 are synthesized by transcription and translation of respective preproendothelin mRNAs into Preproendothelins. Big ET is synthesized by proteolysis of Preproendothelins. Following, Endothelin converting

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enzymes converts Big ET to ET. Endothelins play a role by interacting with their respective receptors [21,22].

The family of endogenous endothelin peptides consists of 21 aminoacid peptides which have high level of homology , similar structure. ET1, ET2 and ET3 genes are situated on chromosomes 6, 1 and 20 respectively [22]. ET1 has been identified in the endothelial cells of arteries and veins. It has prominent role in controlling perfusion of all organs [23]. As shown in figure-1a, ET1 levels is mainly based on transcription of gene ET1, which encodes preproendothelin1, is regulated by number of factors both physical and chemical stimuli [24]. Preproendothelin1 is cleaved by Furin like endopeptidase into bigET1(38 amino acids). Biologically active ET1 (21 amino acids) is produced by endothelin converting enzyme (ECE) [22-24]. ET1 secretion is stimulated by both physical and chemical stimuli like stress, hypoxia, ischemia, reactive oxygen species, vasoactive peptides, growth factors, certain lipoproteins, cyclosporine, and endotoxin. ET1 production is inhibited by Endothelium-derived NO, natriuretic peptides, vasodilators, prostaglandins and heparin [25].

Mechanism of Action

ET1 signals takes place by two G-protein coupled ET receptors - ETA and ETB. ETA predominantly found in the smooth muscle promotes vasoconstriction (figure 1b). ETB receptors are located in the endothelial and smooth muscle cells and their activation causes vasodilatation by the release of vasodilators acting on smooth muscles [26,27]. Binding to ETA receptor causes vasoconstriction which causes increased Ca2+ influx and can produce reactive oxygen species (ROS) [28].

On the other hand, ETB receptors present on the endothelium cause signalling of ET1, in an autocrine manner which stimulates the nitric oxide synthase (NOS) and synthesis of NO. This stimulation acts as the vasodilatory component [29]. Hence there is a balance of ET1 mediated control on vascular tone with vasodilation which promotes regulation of blood pressure during pregnancy. Aberrant signalling of these receptors can cause vasoconstriction leading on to hypertension in PE. Furthermore, ETB has the ETB-mediated-clearance, which causes clearance of the ET1 in the system which is about 80%. [30].

Role of Endothelin 1in Preeclampsia

Sl no	Authors, Place of study and year	Observations	P value	Method of estimation
1.	TAYLOR RN et al., *USA,* 1990	Potent vasopressor endothelin may be released from injured endothelium in preeclamptic women contributing to vasospasm.	<0.01	Immunoreaction
2.	Nishikawa S et al., Japan, 2000	Increased production of ET leads to vasoconstriction	<0.05	RIA
3.	Baksu B et al., London, UK, 2005	Increased vasomotor tone due to imbalance between NO and ET1	<0.001	RIA
4.	Aggarwal PK et al., Chandigarh, India, 2012	Increased levels of sFlt-1 and sEng can release ET1 from endothelial cells, acting directly on them or indirectly by reducing the availability of VEGF leading on to hypertension and proteinuria.	<0.001	ELISA
5.	Karakus S et al., Turkey, 2015	Elevated ET1 as biomarker of endothelial dysfunction	ET1 higher in cases but not reached statistical significance. P>0.05	ELISA
6.	Singh A et al., India, 2015	Possible existence of interplay in positive feedback mechanisms by which cytokines cause release of ET1 or vice versa contributing to endothelial dysfunction systemically.	<0.001	ELISA
7.	Verdonk K et al., The Netherland, 2015	ET1 elevation is determinant of increased blood pressure, proteinuria, and causes RAAS suppression	<0.001	ELISA
8.	Lind Malte A et al., UK, 2018	There may be link between anti-angiogenesis and ET1 up regulation	<0.001	ELISA

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9.	Tamada S ET AL., Japan, 2019	Intracellular signalling of pro-renin receptor causes production of ET1 leading to vasoconstriction.	<0.05	ELISA
10.	M.K. Simanjuntak et al., Indonesia, 2021	Decreased serum level of prostacyclin and NO causes increased ET1 which leads to smooth muscle sensitivity leads to peripheral vascularity and vascular hypertrophy.	<0.05	ELISA

Table 1. Summary of major (case – control) studies assessing the circulating ET1 in Preeclampsia.

Several studies have reported the importance of circulating ET1 levels in relation to endothelial dysfunction in PE (Table 1). These studies have revealed that circulating ET1 levels are high in preeclampsia than normal pregnancy.

In a healthy normal pregnancy, cytotrophoblasts of foetal origin invades maternal spiral arteries transforming into endothelial-like cells. This remodelling transforms the normal low-capacitance, high-resistance maternal spiral vessels high-capacitance, lower resistance vessels. However, in preeclampsia, the failure to remodel leads to insufficient blood flow to uteroplacental unit causing poor placentation [41].

Endothelin 1 and oxidative stress

Because of poor placentation, there would be repeated episodes of placental hypoxia and reperfusion injury culminating in damage to endothelium. Hypoxia leads to increase in the production of ROS, causing oxidative stress [42]. As a result there would be overproduction of placental factors like soluble endoglin, soluble fms-like tyrosine kinase-1 (SFlt-1), Tumour Necrosis factor alpha and agonistic antibodies against Angiotensin II type I receptor (AT1-AA). Entry of the above factors into the maternal circulation leads to dysfunction of maternal vascular endothelium, causing enhanced synthesis of vasoconstrictors (ET1) [45]

Maternal ET1 released by endothelial cells and syncytiotrophoblastic cells of placenta implicates for activation of key signalling molecules and induce oxidative stress and endoplasmic reticulum stress in pre-eclampsia

Endothelin 1 and Angiogenic origin

Studies from the past suggest link between anti-angiogenesis and ET1 upregulation. Decrease in the placental perfusion results in hypoxia and release of soluble Fms-like tyrosine kinase-1. SFlt-1 binds to vascular endothelial growth factor which is free. When production of ET1 is turned on it stimulates blood pressure, protein in urine and suppresses release of renin. Such suppression is also possible when there is hypertension. The renin suppression happened when it is parallelly with aldosterone suppression. This diminished activity by the RAAS with hypertension causes reduction in volume in circulation and decreases placental perfusion.ET1 induces release of sFlt-1 from the placenta, causing harmful feed-forward mechanism [24].

Endothelin 1 and Uteroplacental origin

ET1 is synthesised from endothelial cells, while its mRNA is detected in human placenta as well. mRNA expression in Trophoblastic ET1 is higher in PE than in control subjects [46]. Their report suggests that the enhanced production of ET1 from placenta can be the reason for the elevated levels in PE [47]. Few other studies have also reported elevated ET1 levels in amniotic fluid and blood vessels in patients compared to pregnant healthy women [48,49].

Endothelin 1 and Immunogenic origin

In PE due to poor utero-placental perfusion, innate immune response increases production of Tumour necrosis factors (50). TNF-α and IL-2 activates ET1 pathway while IL-6 inhibits endothelium dependent NO, cyclic guanine monophosphate and NO mediated endothelial relaxation which leads to development of systemic hypertension in PE. Additionally, it derranges feto-placental circulation. These above results may help to conclude that ET1 can be a key player connecting primary placental aetiology and secondary systemic dysfunction of the endothelium. While, ET1 along with inflammatory cytokine levels can act as a prognostic profile predicting the likelihood of development of pre-eclampsia (36).

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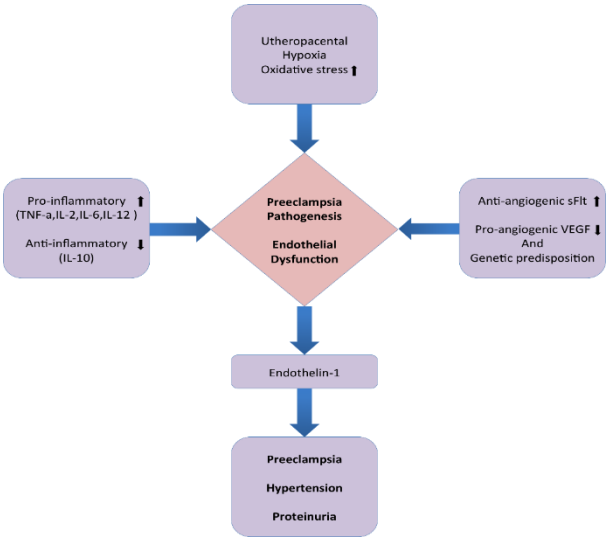

Figure 2: Diagrammatic presentation of Role of Endothelin 1 in pathogenesis of preeclampsia.

ET- receptors – potential therapeutic targets

Binding of ET1 to type A (ETAR) or type B (ETBR) receptor on smooth muscle of blood vessels causes constriction and cell proliferation but ETBR activation on endothelial cells can cause vasodilation because it releases nitric oxide and prostacyclin's. Preeclamptic women show down regulation of ETBR expression in vascular endothelium (51).Antagonistic effect of ET1 on endothelin receptor alleviates maternal preeclampsia symptoms while It improves growth of fetal in animal studies (52).

However, in animal models when developmental toxicity studies were conducted severe teratogenic effects were observed, majorly in craniofacial and cardiovascular leading to malformations, in those offspring's treated with ERAs during pregnancy. The results from animal studies have shown arguing results when compared with clinical trials in conducted in women with pregnancy (53).

This treatment option cannot be considered feasible in pregnancy women as this is known to cause embryonic side effects of endothelin receptor antagonists which are toxic. (54,55) Thus, promoting further research to ensure the safety of maternal and child health.

Additionally, we need to determine whether to block ET receptor A, B, or both. Alternatively, example one could concentrate on the underlying causes of the ET1 increase (e.g. sFlt-1) which could lead to newer treatment options, such as the removal of sFlt-1 through apheresis. (56).

Experimental models of PE

ET1 is an independent determinant for increase in blood pressure and proteinuria in PE based on multiple regression analysis. Moreover, in experimental animal models it is found that PE is responsive to ET type-A receptor antagonism. Recent studies propose that aberrant ETB receptor signalling may have a pivotal role in PE (30).

Despite the involvement of various pathways like interplay between angiogenic factors and maternal immune response, the endothelin-1 system seems to be a common end pathway in the pathogenesis of PE (57).

Study analysis suggested that high soluble FM's-like tyrosine kinase-1 levels causes induction of ET1 synthesis, which contributed to the hypertension and proteinuria and also decreased the renin and aldosterone. Therefore, ET1 plays a crucial role in the pathogenesis of preeclampsia, suggesting that targeting ET1 activation or its effects could be beneficial in treating this disease (37).ET1 is supposed to be a potent inducer of placental ER stress in early-onset preeclampsia. With proven benefits of ETAR antagonists in gestational hypertension, supplementing ETB antagonists can enhance the benefits by decreasing placental ER stress (13).

In recent years, several animal models for experimental preeclampsia have been developed in order to obtain a better understanding and for establishing the causes. Relationships of such factors in the pathophysiology have been postulated in human preeclampsia. It is clear that hypertension seen in reduced uterine perfusion pressure (RUPP), placental ischemia model is heavily dependent on increased ET1 production and signalling through the ETA receptor.

Conclusion:

This study suggests that circulating ET1 may have a crucial role in the pathogenesis of preeclampsia. In view of an association between circulating endothelin levels and oxidative stress, endoplasmic reticulum stress path way, angiogenesis, and clinical hypertension, suggests that endothelin is a pathogenic juncture of endothelial dysfunction in preeclampsia.

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