Endothelin-1 - A Review

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In recent times there has been considerable speculation as to the mediators of vascular spasm and endothelial injury in pregnancy induced hypertension. These two factors compounded with platelet aggregation aggravate the situation ultimately resulting in the syndrome known as Pregnancy Induced Hypertension (PIH). PIH has many features common with conditions like Disseminated Intravascular Coagulation (DIC). Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP). All these four conditions have two pathological features in common. These are retardation of the blood flow with reduction of tissue perfusion and endothelial injury leading to migration of colloids into the tissue spaces.

The final result in PIH is almost certainly on the endothelial cells. It would be interesting and to some extent challenging also to speculate on the mediators of endothelial injury. The various mediators investigated till recently have been fibronectin (Stubbs et al 1986) and (Lazarchick et al 1996), antithrombin-III (Weiner and Brandt 1982), arachidonic acid metabolities (Walsh and Parisi 1986) (Moddley and Reddi 1984) (Brown et al 1987), Nitric Oxide (Neri et al 1995), lipid peroxide and finally endothelin (Taylor et al 1990). These are the various circulating factors which show considerable changes in PIH. As for example the level of fibronectin keeps on mounting in PIH and has been used as a marker for predicting the onset of PIH and has been used as a maker for predicting the onset of PIH in late pregnancy. However the fibronectin appears to be a result rather than the cause of endoethelial injury. Similary antithrombin-III shows a decline in PIH to keep a check on the progressive platelet aggregation in a desperate attempt to maintain the cirulation. Reduction of prostacyclin and increase of thromboxane A_2 are probably the effect of endothelial injury. Most exciting factor amongst these mediators in recent times has been the role and status of nitric oxide in PIH. It is postulated that the endothelial injury sustained primarily due to the metabolites released from ischaemic placental bed leads to the reduction of nitric oxide in vascular system due to endothelial injury. It is now almost confirmed that reduction of nitric oxide is responsible for aggravation of the effects of thromboxin A_2, platelet aggregation and vasopasm due to lack of CGMP which is a most potent vasodilator. Lastly it would be interesting to discuss the role of endothelin in PIH.

Endothelins : In this presentation it is proposed to look at the biochemistry and genesis of endothelial injury with its role in the liberation of endothelin.

Bio-Chemistry of Endothelin: Endothelins are a family of vasospastic peptides. These are present in three isopeptide forms:

endothelin-1, endothelin-2 and endothelin-3. Each one is encoded by a separate gene (Inoue et al 1989).

Sources of Endothelins : Endothelins have been found in

a. Endometrium
b. Endothelial cells
c. Glomerular epithelial cells.

Characteristic Properties of Different Types of Endothelin-1:

Endothelin-1: Endothelin-1 is formed in a stepwise manner: Preproendothelin (23 amino acids) is cleaved to liberate proendothelin (39 amino acids). Proendothelins or "big endothelin-1" are then cleaved by a membrane - bound endothelin - converting enzyme (ECE) to form endothelin-1 (21 amino acids) (Yanagisawa et al 1988). Although endothelins are not produced by neutrophils, neutrophil cathepsin can convert the 39 amino acid precursers to its 2 amino acid active form (Mc Millen et al 1995) the ultimate mediators of vasospasm (Fig. I).

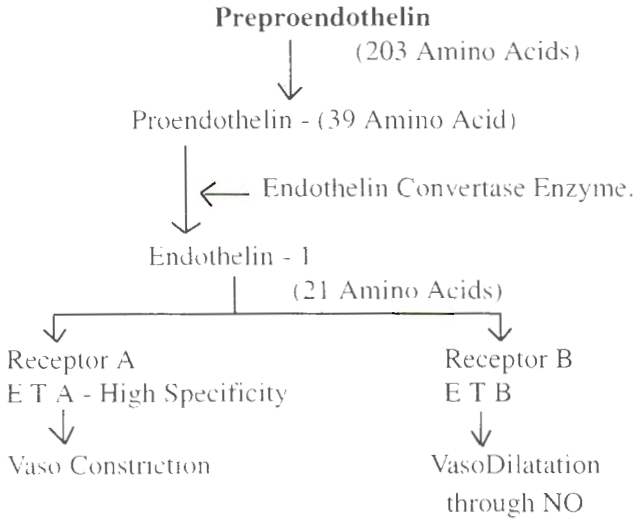

Fig I

Endothelin-1 is the most potent vasoconstrictor of vascular smooth muscles. This is brought about by the influx of extra cellular Calcium initiating the smooth muscle contraction. Nitric Oxide inhibits the vasoconstrictive effect of endothelin-1.

Endothelin Receptors : Two types of endothelin receptors have been described, endothelin receptor-A (ETA) and endothelin receptor-B (ETB). ETA shows a high specificity for endothelin-1 and promotes the vasoconstrictive effect whereas ETB has less affinity and perhaps modulates the release of nitric oxide with subsequent vasodilation (Leppaluoto and Ruskoabo 1992).

This observation has raised an issue of utilising the endothelin level in early pregnancy for predicttion of PIH. Some workers have worked in this area and the possibilities of a predictive index appear to be strong. In this context it is relevant to note that the infusion of magnesium sulfate reduces the endothelin-1. However this effect was not observed in normotensive pregnant women.

Mechanism of Vaso Spasm due to Endothelin:
As endothelin-1 levels increase phospholipase C which is activated and this inturn cleaves the inositol triphosphate(IP3) which causes calcium release from endoplasmic reticular stores of calcium (McMillen et al 1995). After release this influx of calcium leads to smooth muscles activity and vasospasm (Fig-II.)

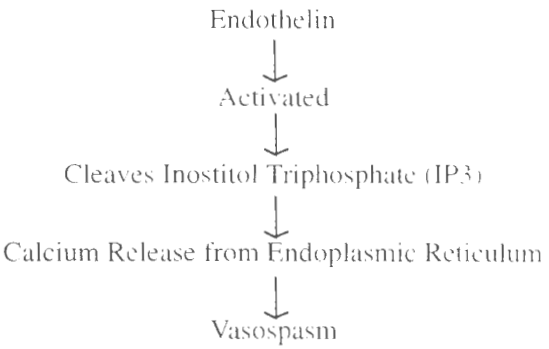

Fig II

Effect of selective E T A Receptor Antagonist :

Agents Binding with Different Receptors

ETB + Sarafotoxin - Vasodilatation
(Agonist)

ETA & ETB → Bosentan Antagonist → Decreased Mean Aortic Pressure
↓
More Effect on ETA

Fig III

BQ 1 2 3 and (Fig.III) Sarafotoxin S6c agonist of E T B leads to a dose dependant increase in pulmonary blood flow and a decrease in peripheral vascular resistance. Stimulation of E T B with Sarafotoxin S6c results in vasodilation. These findings lead to the conclusion that E T B opposes the vasodilation. E T B receptor probably act through nitric oxide / cyclic GMP pathway activation and causes the vasodilation (Ivy et al 1994).

Effects of Endothelin on Peripheral Vascular System: In an exciting study the agent Bosentan had been experimentally used to observe the effects on endothelins. This substance has got the property of binding with both E T A and E T B receptors as antagonist to both the receptor types. But in between these two binding with E T A is more (Adachi et al 1994). In experimental study this substance was injected to the healthy dogs simultaneously repeating the same procedures in experimental hypertensive dogs. In the healthy normotensive dogs Bosenton decreased mean aortic pressure by 38mmHg indicating predominance of E T B binding. When Bosentan was administered to experimental hypertensive dogs the animals registered increase of endothelin-1 levels with rise of blood pressure (Donckier et al 1995).

Effects of Proendothelin-1 in Men: Haynes and Webb (1994) infused proendothelin-1 into the brachial artery of 18 men. Contrary to the expectation the vasoconstriction was absent when simultaneously a metalloprotease inhibitor of ECE, phophoramidon was used. Interestingly when infused alone, phophoramidon produced 37 percent increase in blood flow, but did not effect the response to endothelin-1.

Summary of Experimental Evidences with Regards to Endothelin-1:

Endothelin-1 may initiate the pathogenesis of vasoconstriction in pregnancy induced hypertension a fundamental basis of PIH. However the other confounding factors are that infusion of endothelin-1 resulted in only moderate increase of blood pressure (Vierhapper 1990). Also the neutralising antibodies to the endothelin do not lower the blood pressure (Takagi et al 1991). Belfort et al (1996) observed increase in the tone of omental arteries in normotensive nonpregnant patients, normal pregnant patients and patients with PIH. The degree of increase in vascular tone following infusion of endothelin-1 was some in all these groups.

Nitric Oxide and Endothelin-1:

A. Inspite of the fact that nitric oxide and endothelin-1 have opposing effets it is interesting to note that nitric oxide exerts its relaxing effect on vascular smooth muscles through binding with ETB first before the effect of CGMP dilatation of blood vessels. However it is understandable that ETB receptor has an opposing effect to the ETA receptor binding for endothelin-1.
B. Nitric oxide has been shown to suppress the biosynthesis of endothelin-1 (Kourembancs et al 1993).
C. Endothelin-1 and nitric oxide may play a very important role in the final common pathway for preeclampsia / eclampsia / Hellp syndrome as well as sepsis with DIC, HUS, TTP.

Endothelial injury by endothelin-1:

It has been known that the trophoblastic invasion occurs after normal inplantation of embryo in two waves. In incomplete invasion patients are destined to develop PIH in late pregnancy. The marker of trophoblastic invasion is the expression of different classes of surface adhesion receptors for extra cellular (Fig.IV) matrix proteins which form the component parts of trophoblastic cellular antigen. This new antigen from father and exposure to trophoblastic cells expressed by the conceptus would possibly alter the immune response of the mother. The effect is accentuated by the augmented release of the endothelial cells into the maternal circulation following partial invasion of myometrial arterioles. This type of release of endothelial cells is known as the residual endothelial shedding.

Sequence of Events Following incomplete trophoblastic invasion

↓

liberation of extracellular matrix protein

↓

Binding with surface adhesion receptor

↓

Plus

↓

Conceptus Antigen ⟶ Alters

Immune Response
No Suppression Effect
Rejection of Allograft
Release of Endothelial Cells

Fig IV

Effects of Endothelial Shedding :

It has been shown that there is a colonization of decidual basalis by macrophages and nonlymphoid granulated lymphocytes of CD-56 and CD-16 variety. These cells secrete tumour growth factor-B (TGF-B) which has an immune suppressive effect protecting the trophoblasts against the effect of natural killer (NK) cells through recognition and tolerance of the paternal component of foetal HLA fraction (Clark et al 1994). Any suboptimal trophoblastic invasion of vascular endothelium may lead to disruption of this protective sequence

The sexual relation before conception is associated with exposure of the maternal genitalia to seminal plasma which is immunogenic as proved by occasional posteoital anaphylaxis. Some of the seminal plasma antigens are similar to the antigens expressed by trophoblasts (Kajino et al 1988). It is normally expected that this phenomena of exposure to seminal plasma proteins will lead to T cells sensitization and antibody formation in wife. However this response may vary in different individuals. In the maternal system there are receptors for recognition of antigens of MHC class-II. The binding of the seminal plasma antigens to these receptors on the maternal system and the antigen presenting cell of the female partner would mean the confirmation of HLA antigens lacking in human trophoblast. This ultimately leads to immunosuppressive effect following the exposure of the vaginal mucosa and endometrium to paternal antigen present in the semen. This suppression of response to the paternal antigen may follow frequent exposure of the maternal system to the seminal plasma after frequent sexual intercourse. This is confirmed by the fact that blocking the exposure of vaginal mucosa to seminal plasma by condom may result in increased incidence of PIH in the conception following the discontinuation of the barrier method of contraceptive procedure (Klonoff et al 1989).

Immunological Effects of Residual Endothelium following incomplete invasion of trophoblast: (Fig V) The residual endothelium after incomplete invasion of myometrial vessels could trigger the sequence of events in the pathogenesis of PIH. The vascular cell adhesion molecule-1 (VCAN-1) is produced through stimulation of endothelium by interleukin-1 beta (IL-1B) tumour necrosis factor alpha (TNF alpha) and interferon (Kajino et al 1988). VCAM-1 promotes neutrophil activation and subsequent endothelial injury as measured by the rising concentration of neutrophil elastase. This development leads to neutrophil cathepsin which may convert the endothelin-1 from proendothelin and activation of endothelin-1. These events are simultaneously associated with increase in the level of interleukin-6 (IL-6) and fibronectin (Klonoff et al 1989).

Immunological Response to Endothelial Shedding

Normal	Abnormal
↓	↓
Exposure to seminal Plasma	No Supression
↓	↓
Altered T Cell Behaviour	Reject Response by Stimulation of Endothelium by IL-1 B, TNF -£ Interferon
↓	
Tolerence to Foreign Antigen	
↓	
Supression of Reject Response	

Fig V.

Effects of Endothelial Injury : Endothelin-1 released after endothelial injury activates the phospholipase A, C, and D stimulating the arachidonic acid pathway and proteinkinase C. However the subsequent developments

leading to PIH after the liberation of endothelin have not been properly understood. But it is postulated that there is a lack of immune tolerance between the couples during conception following short exposure to seminal plasma may set the stage for endothelial damage in the decidual bed as a result of incomplete trophoblastic replacement of native endothelium in decidual arterioles.

Conclusion:

The extensive research work carried out to come to a conclusion with regards to the etiopathology of PIH has unfortunately not solved the problem yet. But one fact emerges clear out of these observations and that there are two sets of factors operative in the pregnant subject particularly primigravidae - one set attempting to bring about relaxation of blood vessels, refractoriness to vasopressor agents and increase of blood flow to the placenta and foetus while the other set of factors following inadequate trophoblastic invasion of decidual arterioles unable to cope with the increased demands for blood supply sets in ischaemic states triggering off abnormal metabolite like lipid peroxide and free radicals which tend to damage the endothelium of blood vessels. In this scenerio on the one hand nitric oxide and prostacyclin to keep the tissue perfusion at an optimum state whereas the other factors like endothelin, serotonin and thromboxane A_2 tend to produce vasospasm and aggravate peripheral resistance thereby elevating the blood pressure. Possibly in near future the scientists and clinicians would be in possession of vascular relaxing factors ensuring survival and growth of the foetus in utero. In this presentation a relatively detailed account of yet another vasoactive agent endothelin-1 has been presented.

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