Does nitric oxide play a role in normal pregnancy and pregnancy-induced hypertension?

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Introduction

Haemodynamics of gestation are characterized by a high cardiac output, low resistance state. Concomitantly the pressor response to administration of vasoconstrictors like noradrenaline and angiotensin II is blunted.

Which factors are responsible for this state of vasodilatation and altered pressor responsiveness? Paracrine products of the vascular epithelium are key candidates to explain the circulatory abnormalities. Historically, prostaglandins were first thought to be involved, but more recently attention has focused on a novel endothelium-derived vasodilator, i.e. nitric oxide.

What is the evidence?

Urinary excretion of prostaglandin increases in pregnant women and animals. Some evidence against a major role of prostaglandins is provided by studies in which cyclo-oxygenase inhibitors failed to affect renal haemodynamics or observations on refractoriness to vasopressors in pregnant animals. The case of nitric oxide (NO) is more compelling [1]. NO is generated by endothelial type II nitric oxide synthase and acts via stimulating soluble guanylate cyclase. Constitutive low-level release of NO is a feature of endothelial cells and good arguments have been offered that it participates in the control of resistance of vascular bed and overall control of blood pressure.

In the past 2 years some evidence has accumulated which strongly suggests that NO is also related to gestational vasodilatation during pregnancy. More fragmentary information also implicates deficiency of or impaired responsiveness to NO in the genesis of pre-eclampsia.

In the following we review the facts and present some hypotheses.

Is nitric oxide involved in the circulatory changes of normal pregnancy?

Increased production of NO is suggested by the observation that urinary excretion of NO2/NO3, derivatives of NO, increases under basal conditions in pregnant rats [2-4]. At a given dose L-NAME, an inhibitor of NO synthase, decreased NO generation significantly less in pregnant rats than in virgin rats [2]. This observation would be compatible with the idea that synthesis of NO is increased during pregnancy. Excess production of NO might also explain the blunted response to noradrenaline characteristically seen during normal pregnancy. Inhibition of NO production by L-NMMA abolished the blunted pressor response to noradrenaline in the pregnant rat, while it has no significant effect on the pressor response in the virgin rat [5].

Information on the role of NO in normal human pregnancy is scarce. It is known, however, that the placenta is capable of generating NO and of responding to NO. Immunohistochemical studies revealed endothelial NO synthase in the endothelial cells of umbilical cord arteries and veins, although positive staining was only found in approximately 50% of the veins [6]. In vitro, histamine, a stimulator of NO release, relaxed umbilical arteries dose-dependent in early gestation (from the 18th to 32nd week), but not late gestation (from the 38th to 41st week). This finding suggests that with increasing duration of gestation, either less NO is generated or the response to NO is attenuated [7]. The endothelial isoform of NO synthase is demonstrable in the resistance vessels of the placenta, but not in the endothelial cells of the capillaries of the terminal villi, which are devoid of smooth muscles. What is the role of NO? It may contribute to the function of the syncytiotrophoblast as an endothelial barrier and may be secreted towards the intervillous space, or else it may be involved in signal transduction [6].

Is impaired generation of nitric oxide involved in pregnancy-induced hypertension?

Pregnancy-induced hypertension is characterized by two abnormalities, (i) increased systemic vascular res-
istance, and (ii) contracted plasma volume. In parallel, the response to vasopressor agents is exaggerated. It is plausible to assume that these abnormalities are related to an imbalance in the synthesis of vasoactive agents and that such imbalance is related to endothelial cell damage [8]. Is this working hypothesis consistent with available information?

In the pregnant rat chronic blockade of NO synthesis not only suppresses vasodilatation, but also increases blood pressure, induces proteinuria at the end of pregnancy, and reduces expansion of the maternal plasma volume space [9]. At a recent meeting, the 9th International Congress of the International Society for the Study of Hypertension in Pregnancy, Sydney, 1994 (abstract book A.B.), a number of studies were reported which further support a role of NO. In baboons inhibition of NO synthase caused a slight increase in MAP mainly in middle or late pregnancy (Henessy et al., A.B. p. 64). In rats with adriamycin nephropathy, pregnancy enhanced blood-pressure and urine protein excretion without hyperfiltration. Treatment with L-arginine normalized MAP and increased GFR, suggesting inadequately diminished synthesis of NO during pregnancy [10]. The above hypothesis is also supported by the observation that chronic blockade of NO synthesis had no pressor effect on the pregnant rat with adriamycin nephropathy in contrast to the normal pregnant rat (Podjarny et al., A.B. p. 309). In pregnant rats, chronic blockade of NO synthesis caused fetal growth retardation (Salas, A.B. p. 162).

In contrast to these animal studies, the results of which seem to fit the hypothesis beautifully, data regarding NO in women with pregnancy-induced hypertension are more conflicting. NO synthase in the placenta has been found to be reduced in pre-eclampsia (Brennecke et al., A.B. p. 87) as well as the release of vasodilators (EDRF) from umbilical vessels [11]. However, increased plasma and urine metabolites of NO were found in women with pregnancy-induced hypertension (Davidge et al., A.B. p. 164). Cameron et al. [12] found a significant correlation between the changes in systolic blood pressure and urinary NO excretion.

Where do we stand today?

Experimental data leave no doubt that generation of NO is increased in normal pregnancy. Convincing evidence is provided by the observation that chronic inhibition of NO synthesis causes hypertension and fetal growth retardation implicating a role of NO in development and maintenance of gestational vasodilatation and refractoriness to vasopressors. No convincing data are so far available with respect to human pregnancy, although some evidence is at least consistent with a role of NO in the placental circulation.

The role of NO is not only suggestive of systemic vasodilatation (mainly in the first 2/3 of pregnancy), but also in the pathogenesis of pregnancy-induced hypertension. Some reports on high NO production might be explained by the postulate that seemingly high levels are inadequate to offset vascular contraction.

What may be the cause of inadequately low NO? Pregnancy is a state characterized by low plasma levels of L-arginine. This is the result of increased transfer of amino acids to the fetus [13]. Relative deficiency of the precursor, in the presence of systemic endothelial damage, may cause insufficient synthesis of the product, i.e. NO (or EDRF). This assumption might explain the recent observation that oral treatment with L-arginine lowers blood pressure and increases GFR in pregnant rats with adriamycin nephropathy. Administration of L-arginine also ameliorated a syndrome of intravascular coagulation resembling pre-eclampsia which was induced by administration of lipopolysaccharide [4]. It is conceivable that even increased levels of NO in hypertensive pregnant women (Davidge et al., A.B. p. 164, 12) may be insufficient to overcome the state of vasoconstriction.

Further studies are required to prove this hypothesis and to examine whether a relationship exists between the degree of pre-eclampsia and impairment of nitric oxide synthesis. Since endogenous inhibitors of NO synthase, asymmetric dimethyl-L-arginine accumulate in renal failure, this hypothesis may also provide an explanation of why women with renal impairment are so prone to pre-eclampsia [14].

References

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Ischaemia and reperfusion injury in the kidney: current status and future direction

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Introduction

Both the interruption and subsequent restoration of blood flow (reperfusion) can cause tissue injury in any organ although the consequences vary greatly. The impact is most dramatic in the heart where coronary artery disease, leading to myocardial necrosis, contractile failure, and arrhythmias, is responsible for over one million deaths per year in the European Community alone. Cardiologists have become increasingly successful at developing experimental interventions to protect and preserve the myocardium. Some of their strategies could be applied to the kidney, where ischaemia and reperfusion contributes to the non-immunological damage that complicates transplantation, revascularization procedures, and periods of hypoperfusion.

Severe reduction of renal blood flow causes cell damage by high-energy phosphate depletion and the subsequent failure to maintain physiological ion gradients across the cell membrane. The severity of injury depends on the duration of ischaemia and the availability of a collateral circulation, although paradoxically the restoration of blood flow is itself associated with further tissue damage called reperfusion injury. When blood supply to the kidney is compromised, flow is diverted from cortex to medulla which preserves oxygenation of the metabolically vulnerable medulla, at the expense of cortical perfusion and glomerular filtration (GFR). Reperfusion with oxygenated blood is associated with free radical generation, leading to lipid peroxidation, polysaccharide depolymerization and deoxyribonucleotide degradation. Injured endothelial cells fail to vasodilate underlying vascular smooth muscle, release potent vasoconstrictors, and swell, which leads to increased permeability. The combination of vasoconstriction, cell swelling, extracellular oedema, and finally, leukocyte and platelet trapping by the activated endothelium, leads to progressive loss of perfusion. Following sublethal injury the mechanism behind cellular recovery remains a mystery but the increased expression of heat shock proteins, 'molecular chaperones', may be involved in this cytoprotection and repair of cytoskeletal structures. Some of the steps in this sequence of events have been successfully targeted by cardiologists; we will discuss these interventions and their implications for renal injury following ischaemia and reperfusion.

This could involve small molecules...

Adenosine

The corticomedullary shunt, which still occurs in the denervated kidney, could be explained by the release of adenosine from ischaemic endothelial and parenchymal cells, due to their failure to recycle adenine nucleotides. Adenosine promotes the redistribution of blood flow by causing afferent arteriolar vasoconstriction (via A1 receptor activation), efferent arteriolar vasodilatation (via A2 receptors), and medullary vasodilatation (via A2 receptors). This heterogeneity in vascular reactivity of adenosine receptors is unique to the kidney although A1-mediated cortical vasoconstriction is dominant. In the heart, in contrast, adenosine directly protects the cardiac myocyte by activation of non-vasoactive A1 receptors and vasodilates via A2 receptors. In the kidney, reversal of the corticomedullary shunt by a selective A1 antagonist might be appropriate, although benefit from improved perfusion would depend on ensuring adequate oxygen delivery to the kidney. Pretreatment with theophyllines (non-specific adenosine receptor antagonists) has already been shown to diminish the reduction in GFR following either experimental renal ischaemia or exposure to glycerol.

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