Nitric Oxide in Obstetrics

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Introduction

A noxious unstable gas is an unlikely candidate to act as a biological messenger. However, in the last decade, NO, a byproduct of automobile exhaust, electric power stations, lightening and cigarette smoke, was discovered in the body, where it participates in various functions, including suppression of pathogens, vasodilation and neurotransmission (Lowenstein et al, 1994).

The NO radical appears to be part of a ubiquitous autocrine paracrine signalling system, being synthesized and acting in many tissues including endothelium, vascular smooth muscle, macrophages and platelets (Moncada et al 1991). NO is an inorganic free radical gas, shown to possess more potential biological function than any known molecule. It is thus called "Molecule of the Century" (Das Gupta 1997). It has important vasoactive function related to its ability to inhibit platelet aggregation and to relax perivascular smooth muscles. NO also functions as a neurotransmitter and has been implicated in the pathogenesis of a spectrum of diseases, including septic shock, & chronic hypertension. It has an unpaired electron in its outer orbital, making the molecule highly reactive with a very short half life of few seconds.

NO is synthesized from L-arginine (Palmer et al, 1988, Schmidt et al, 1988) by a family of enzymes known as nitric oxide synthases (NOS). Three isoforms of NO have now been identified; of these the endothelial and neuronal isoforms are constitutive, i.e. they are always present. Endothelial isoforms is consistently formed in vascular endothelium, platelets, endocardium & myocardium and neuronal isoforms which acts as neurotransmitter in the non-adrenergic and non-cholinergic nervous system are also constitutive isoforms. These nitrergic nervous system or nitretic nerves may play an important role in dilatation of certain blood vessels and also relaxation of G.I. Tract sphincters. These isoforms are activated by a flux of calcium into the cells. The main site of third isoform known as inducible isoform is found in the macrophages and is produced in response to stress, particularly infection, endotoxins, exotoxins or cytokines and TNF. It is relatively independent of calcium for its activity. NO thus liberated in these conditions reacts with superoxides and hydrogen peroxides forming peroxynitrite which combines with tyrosine forming a highly toxic nitro tyrosin residue.

No in Pregnancy

It is basically responsible for relaxation of smooth muscles of myometrium, brought about by the formation of NO-CGMP from L-arginine. It is found that myometrial

concentration of NO increases significantly in early pregnancy followed by reduction of NO in myometrium and decidua in late pregnancy (Yallampalli et al, 1993). Thus NO tends to protect pregnancy in the early part, gradually declining in concentration in late pregnancy possibly helping to develop the contractile status of myometrium needed during labour. NOS has been localised in syncytiotrophoblast of human placenta (Conrad et al, 1993). Furthermore calcium-dependant and calcium-independent NOS have been detected in human placental villi.

NO & Vascular Endothelium in Pregnancy

The vascular endothelium in a healthy adult female weighs 1.5 kg (Henderson, 1991, Anggard, 1994) and the total pulmonary vascular endothelium is big enough to cover six football grounds (Morris et al, 1996). It is constantly exposed to humoral factors, inflamatory mediators and changes in shear stress of blood flow. This stress is the greatest stimulus for NO secretion (Pohl et al, 1986). EDRF or NO maintain the following vital functions - monitor haemodynamic & humoral signals, modulate release of vasoactive substances, prevent platelet aggregation by keeping balance between PGI_2 & TXA_2 in favour of PGI_2 (Friedman, 1988). It also inhibits coagulation amd modulates fibrinolysis, increases heart rate, cardiac output, blood volume. It reduces arterial pressure.

No in Pre-Eclampsia

Endometrial cell NO synthesis contributes directly to the maintenance of vascular tone and is an essential component of blood pressure regulation under normal physiologic circumstances (Moncada & Higgs, 1993). In the quest to define the precise pathophysiologic conditions responsible for pre-eclampsia, this endogenous nitro-vasodilator appears to be a likely candidate (Silver et al, 1996). At least three impressions can be gleaned from published laboratory studies.

1. NO plays an active role in maintenance of vascular tone during normal pregnancy.
2. A pre-eclampsia like syndrome with clinical and laboratory perturbations result from NO inhibition.
3. Administration of NO donors after NO inhibition can restore the vascular refractoriness to vasconstrictors that is typical of normal pregnancy.

In vivo studies linking NO to pre-eclampsia are less compelling. Studies designed to identify reduction of NO production in pre eclampsia subjects have provided inconsistent results and may be confounded by non-uniform assay methods (Archer, 1993). Just as it would be inappropriate to link NO-metabolism to human pre-eclampsia on the strength of animal data alone, it is premature to ex clude NO as a possible mediator in this disease. Decreased NO release or decreased production has not been shown to develop prior to the onset of hypertension. Thus, the changes in NO concentrations in women with P.I.H. appear to be the consequence of hypertension and not the inciting event (Morris, 1996).

Rather than suppression of NO-synthesis as a cause of preeclampsia, a blunting or absence of a normal rise in NO-synthesis activity accompanying early gestation may occur in this syndrome. Weiner et al (1994), demonstrated that NO synthase activity increases in a number of maternal tissues early in guinea pig gestation, possibly under the influence of estradiol. If this early adaptation were aberrent, or missing altogether, the vasodilatory state\induced by NO could be compromised, setting the stage for vasoconstrictor sensitivity and in selected patients pre-eclampsia. The absence of a compensatory rise in NO synthesis after hypertension has developed, might also suggest a relative deficiency in production of this mediator as a cause of pre-eclapmsia.

We should nevertheless, be careful not to make the same mistake that was made with PGI_2 in the eighties, when it was assumed that PGI_2 deficiency was the sole explanation for the clinical syndrome pre-eclampsia. Pre-eclampsia is characterised by complex endothelial cell damage and dysfunction which could be linked to similar dysfunctions of normal processess in the syncitiotrophoblast. The

endothelial cell dysfunction results in a disturbance of the delicate balance between vasodilators e.g. PGI_2 & NO on the one hand and vasoconstrictors such as Angiotensin II, TXA_2 and Endothelin on the other. Similarly the balance between platelet stimulating and inhibiting factors has to be considered in the overall picture of this disease.

NO donors such as glyceryl trinitrate (GTN) & sodium nitroprusside have powerful antihypertensive effects in the majority, but not in all patients with severe pre-eclampsia. The limited effect of sodium nitroprusside in some of these patients is an evidence that a deficiency in the NO-pathway is unlikely to be the only mechanism involved in the aetiology of hypertensive disorders of pregnancy.

NO & Fetoplacental Circulation

Several experimental findings, both in human & in animals, have suggested that trophoblast derived NO contributes to the control of placental vascular tone (Hull et al, 1994). Growth retarded fetuses frequently demonstrate reduced, absent or even reversed uterine artery blood velocities during diastole (Trudinger et al, 1985). When Glyceryl tri-nitrite (GTN) is given sublingually there was 21% decrease in the umbilical vascular resistance as was seen in the Doppler umbilical artery flow velocimetry (Giles, 1992). Recently GTN was given I. V. in preclampsia patients between 24 to 26 weeks of gestation and it produced a decrease of both Resistance Index & Pulsatility Index in uterine artery as seen in normal healthy women (Ramsey, 1994). 0.3 mgm of GTN given sublingually can significantly lower the RI (Gruenwald et al, 1994), in both umbilical and uterine arteries of patients with preterm labour. Serum Nitrite/Nitrates & Growth hormones levels could be increased by infusion of L-arginine in IUGR cases without any changes in maternal blood pressure.

NO & Preterm Labour

NO system may inhibit uterine contractility during pregnancy to maintain uterine quiescence (Yallampalli et al, 1996). There is gathering evidence that placental corticotrophin releasing hormone (CRH) acts as a promoter of human parturition. The regulation of placental CRH & NO metabolism has been demonstrated in placental villi; work has shown that NO donors inhibit placental CRH secretion (Sun et al, 1994). This hypothesis was tested in a small, uncontrolled, non-randomised trial at Kings College Hospital (Lees et al, 1994). GTN patches were reported safe, well tolerated & non-invasive. Trials are needed to determine whether there is genuine benefit of NO donors in prevention of preterm labour.

NO in Septic Shock

High levels of circulating bacterial endotoxin & cytokines are a hallmark of septic shock. These result in the induction of inducible NOS in many cells including macrophages, hepatocytes, endothelial & smooth muscle cells of blood vessels. The uncontrolled NO synthesis contributes to hypotension. In addition it also causes venous pooling, cardiac dysfunction, renal impairment, hepatocyte dysfunction which occur as multiple system organ failure developes. Treatment of sepsis in animal with inhibitors of NOS reverses hypotension within minutes (Gryglewski et al, 1989).

Therapeutic strategies with NO

Apart from administration of exogenous NO, manipulation of endogenous NO activity may be used therapeutically. Pharmacological agents increasing endogenous NO activity include Nitro Vasodilators, L-arginine, angiotensin - converting enzyme inhibitors and anti-oxidant drugs. Agents to decrease endogenous NO activity may include corticosteroids & L-arginine analogues which inhibit NOS isoforms. Such drugs are likely to provide significant clinical benefits in the future.

Conclusion

From our school day concept of being a clear colorless

gas which rapidly turns brown on contact with air, nitric oxide has come a long way. The speed of advance in nitric oxide research and the enthusiasm of investigators has meant that excess or deficiency of NO has been linked with many clinical conditions. New approaches to their management and treatment await us.

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