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Regulation of myometrial circulation and uterine vascular tone by constitutive nitric oxide

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ABSTRACT

Pregnancy is a physiological state that involves an increase in uterine blood flow, which is mediated in part by nitric oxide (NO) liberated from the endothelium and nitrergic neurons. The main focus of this review article is to provide information about how endogenous NO regulates uterine and placental blood flow and vascular tone in experimental animals and humans in vivo or in vitro in non-pregnant and pregnant states as well as pregnancy with pre-eclampsia. Uterine arteries from non-pregnant women respond to NO liberated from the endothelium and nitrergic nerves with relaxations, and the release of endothelial NO is influenced by the phase of the estrous cycle, with its enhanced release at the follicular phase when the estrogen level is high. NO bioavailability in the uteroplacental circulatory system is gradually increased during pregnancy. Pre-eclamptic pregnancies with or without intrauterine growth restriction show impaired uteroplacental blood flow accompanied by reduced NO synthesis due to down-regulation of eNOS as well as asymmetric dimethylarginine accumulation and by augmented NO degradation by oxidative stress. Further studies are expected to provide new mechanistic insights into the fascinating process of maternal uterine adaptation in humans and novel prophylactic and therapeutic measures against pre-eclampsia.

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1. Introduction

Sufficient uterine blood flow is essential for normal pregnancy outcome in order to meet the metabolic demand of glucose and oxygen supply in the mother and developing fetus. The pregnancy-associated vascular changes are largely due to alterations in the

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amount/activity of vascular mediators released from the endothelium, smooth muscle, and extracellular matrix. A harmonized network composed of various vasodilator systems, particularly the nitric oxide (NO)-guanylyl cyclase signaling pathway, participates in the uterine hemodynamic adaptations in pregnancy. Hypertension in pregnancy and preeclampsia are major complications and life-threatening conditions to both the mother and fetus, precipitated by various genetic and environmental factors involving uteroplacental hypoperfusion and placental ischemia/hypoxia (Tanbe and Khalil, 2010).

NO is produced when L-arginine is transformed to L-citrulline via catalysis by NO synthase (NOS) in the presence of oxygen and cofactors; Ca^{2+} introduced extracellularly and from intracellular storage sites via stimulation of receptors located on endothelial cell membrane by acetylcholine (ACh), bradykinin (BK) is required for the activation of endothelial NOS (eNOS). On the other hand, shear stress, BK, and insulin induce phosphorylation of $Ser^{1177/1179}$ of eNOS through phosphatidylinositol 3-kinase (PI_3K) and the downstream Akt, serine/threonine protein kinase (PKB), resulting in enhanced NO production (Dimmeler et al., 1999) (Fig. 1). Endothelial NO plays an important role in improving uteroplacental blood flow through changes in vascular tone during pregnancy. Expression of eNOS is increased during pregnancy, leading to increased synthesis and release of NO from the endothelium (Nelson et al., 2000). Estrogen mediates an increase in uterine blood flow via enhanced NO bioavailability with nongenomic- and genomic-mediated mechanisms (Chang and Zhang, 2008). In addition, NO generated from parasympathetic, perivascular nerves (nitrergic nerves) (Toda and Okamura, 1990a, 2003) is expected to contribute to uteroplacental blood flow increase in humans and experimental animals. Improvement of maternal blood pressure and uteroplacental blood flow by enhancing NO-mediated vasodilatation would unravel the intricate association of risk factors involving pathogenesis in pregnancy.

This review will cover information concerning the regulation of uterine arterial tone and blood flow by NO derived from the endothelium and vasodilator nerve in pregnant and nonpregnant women and experimental animals and mechanisms underlying endogenous NO actions in pregnancy in vivo and in vitro. Pathogenesis of clinical and experimental pre-eclampsia in reference to impaired NO synthesis and actions is also discussed, which may help to develop the future approaches in the prophylaxis and treatment of pre-eclampsia and hypertension in pregnancy.

2. Studies on endothelial NO

2.1. Studies in experimental animals

2.1.1. In vivo studies

An up-regulation of eNOS, resulting in increased NO production, contributes to uteroplacental blood flow increases through changes in vascular tone. There is evidence that ACh can release either NO or cyclooxygenase products to cause uterine arterial dilatation in rats and that serotonin-induced uterine vasodilatation is mediated via NO only (Saha et al., 1998). Mice lacking for the gene of eNOS show decreased uterine blood flow (van der Heijden et al., 2005). Physical forces, such as shear stress and stretch, play important roles in the release of NO from the endothelium.

NO is one of the main mediators in the endothelium-dependent pathway for estrogen-induced uterine vasodilatation. Estrogen exerts actions in the vascular endothelium through acute, non-genomic and long term, genomic effects that modulate vascular resistance and blood flow. The uterine blood flow index in trotter mares was maximum on days 5 and −4 during the estrous cycle, estrogen receptor mRNA concentrations increased during days 15 (estrogen receptor α) and −3 (estrogen receptor β), and transcript expression of eNOS correlated positively with blood flow index, suggesting that the uterine vascular eNOS plays an important role in the regulation of uterine blood flow during the estrous cycle (Honnens et al., 2011). Histological studies demonstrated that in the follicular phase, the highest eNOS immunoreactivity was found in the endothelium of arcuate arteries and veins of the pig mesometrium, while immunoreactivity of endothelin-1 (ET-1) was much lower; the highest ET-1

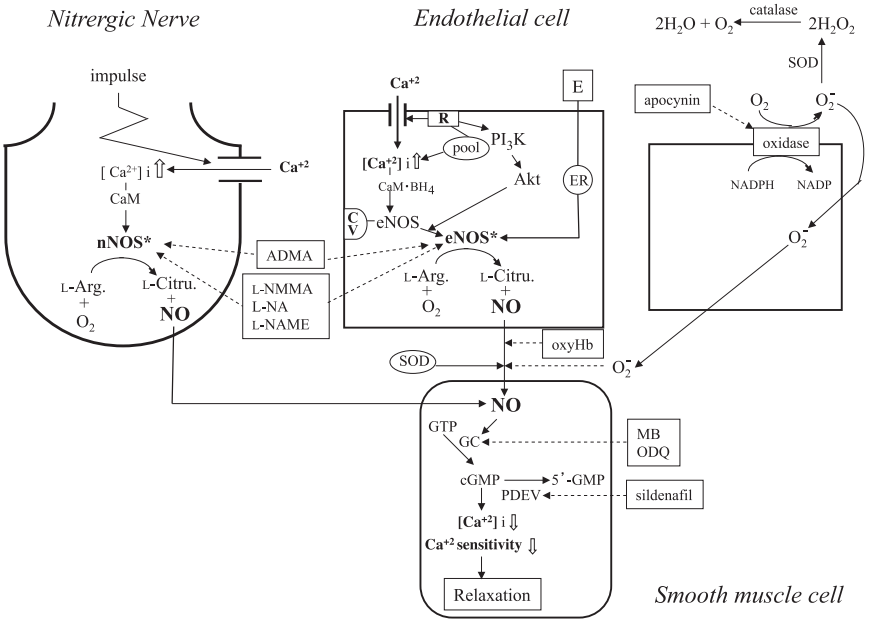

Fig. 1. Information pathways via NO liberated from endothelial cells and nitrergic neurons to uteroplacental vascular smooth muscle. Superoxide anion generation via NADPH oxidase is also included in the upper right figure. R, receptive site on the cell membrane responsible for chemical and physical stimuli; E, estrogen; ER, estrogen receptor; Pool, intracellular Ca^{2+} storage site; PI_3K, phosphatidylinositol 3-kinase; Akt, serine/threonine protein kinase Akt; CaM, calmodulin; BH_4, tetrahydrobiopterin; eNOS*, activated eNOS; nNOS*, activated nNOS*; CV, caveolin-1; L-Arg., L-arginine; L-Citru., L-citrulline; L-NMMA, N^G-monomethyl-L-arginine; L-NA, N^G-nitro-L-arginine; L-NAME, L-NA methylester; ADMA, asymmetric dimethylarginine; SOD, superoxide dismutase; O_2^-, superoxide anion; GC, soluble guanylyl cyclase; PDEV, phosphodiesterase type 5; MB, methylene blue; ODQ, 1H[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one; oxyHb, oxyhemoglobin.

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