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Review: Novel insights into the regulation of vascular tone by sphingosine 1-phosphate

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ABSTRACT

Endothelial dysfunction leading to increased vascular tone is implicated in the pathogenesis of cardiovascular disease, hypertension and pregnancy-related complications like preeclampsia and intrauterine growth restriction. Vascular tone is regulated by a balance between vasoconstrictor and vasodilator signals. Some vascular mediators circulate in blood, whereas others are produced by the endothelium and are delivered to the underlying vascular smooth muscle cells (VSMCs). It is proposed that increased permeability of resistance arteries in preeclampsia allows access of circulating vasoactive factors to VSMCs leading to increased vascular tone. This review focuses on the role of sphingosine 1-phosphate (S1P). This sphingolipid enhances the endothelial barrier, but it can also disrupt the barrier under certain conditions. These S1P-mediated effects on the endothelial barrier have been demonstrated in cultured endothelial cells and in isolated venules. They depend on S1P concentrations, the S1P receptors expressed and the vascular bed. However, no studies have examined if vascular tone is regulated by S1P in resistance arteries through changes in endothelial permeability and the leakage of circulating vasoconstrictors. Our recent studies using the pressure myograph system show that access of infused vasoconstrictors to VSMCs is blocked under low S1P concentrations. Pathophysiological levels of infused S1P disrupt the barrier and maximally increase vascular tone by facilitating access of itself and a co-infused vasoconstrictor to the VSMCs. Interestingly, infusion of an intermediate physiological concentration of S1P showed a small increase in endothelial permeability with controlled leakage of a co-infused vasoconstrictor that led to sub-maximal vascular tone development. These and other studies delineate the important role of S1P in the regulation of vascular tone and emphasize how dysfunction of this regulation can lead to pregnancy-related disorders.

1. Introduction

Dramatic vascular adaptations in pregnancy compensate for the remarkable hemodynamic changes that occur to ensure adequate exchange of nutrients and oxygen at the maternal–fetal interface [1]. All maternal vessels undergo adaptations but the most significant changes are observed in the uterine vasculature. In human beings and many animals, luminal diameters nearly double in size in arcuate, radial and main uterine arteries with little or no vascular wall thickening [2]. In addition to these structural changes, circulating vasodilator concentrations are increased and the sensitivity of uterine arteries to vasodilators is enhanced while the response to vasoconstrictors is generally blunted. This review postulates a role for a circulating bioactive lipid, sphingosine 1-phosphate (S1P), in modulating these regulatory changes in vascular tone.

Under normal physiological conditions, endothelial and non-endothelial-derived vasoactive agents impact vascular tone by acting on both endothelial cells and the underlying vascular smooth muscle cells (VSMCs) [3]. The balance of responses in VSMCs to vasodilator and vasoconstrictor signals regulates vascular tone. Adaptations in this normal balance along with appropriate structural remodeling are essential to maintain appropriate vascular tone during pregnancy [1]. In late pregnancy, there is increased sensitivity to and production of vasodilators including endothelium-derived hyperpolarization factors (EDHF), prostacyclin and nitric oxide (NO). This is accompanied by decreased sensitivity to vasoconstrictors such as endothelin-1, thromboxane A2 and angiotensin II. These changes decrease vascular resistance

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Abbreviations

eNOS	endothelial nitric oxide synthase
ICAM	intercellular adhesion molecule
IL	interleukin
IUGR	intrauterine growth restriction
$[Ca^{2+}]i$	intracellular free Ca^{2+}
NO	nitric oxide
PI3K	phosphatidylinositol 3-kinase
PLC	phospholipase C
PTEN	phosphatase and tensin homolog
ROS	reactive oxygen species
S1P	sphingosine 1-phosphate
$S1P_{1-5}$	sphingosine 1-phosphate receptors
SK	sphingosine kinase
TNF	tumor necrosis factor
VCAM	vascular cell adhesion molecule
VEGF	vascular endothelial growth factor
VSMC	vascular smooth muscle cell

and contribute to the extensive increase in uteroplacental blood flow from baseline at 20–50 ml/min to 450–800 ml/min in late human pregnancy [2]. Numerous factors impact the production and release of vasoactive substances from the placenta and maternal endothelium including hormones and cytokines.

An unanswered question is how circulating vasoactive factors pass across the endothelial barrier of arteries to reach the VSMCs and whether regulation of this process contributes to maintenance of normal vascular tone. We propose that the control of endothelial permeability will govern the access of circulating factors to VSMCs and regulate vascular tone. Moreover, disruption in this mechanism will be found in pregnancies complicated by vascular dysfunction. S1P is a vasoactive mediator and also controls the endothelial barrier [4–6]. This review will describe what is known about these dual roles of S1P in the vasculature and will also outline new findings on the regulation of vascular tone through the control of endothelial permeability by S1P. Potential therapeutics using S1P receptor agonists and antagonists are also discussed.

2. Endothelial barrier structure and function

The endothelium regulates many biological processes including cardiovascular homeostasis, angiogenesis and inflammation. The endothelium also controls the transport of blood components to the surrounding tissues through paracellular and transcellular pathways. The transcellular pathway transports macromolecules across the endothelium through specialized vesicles. In paracellular transport, molecules move passively across the barrier between the endothelial cells [7].

Endothelial cells are connected to each other by adherens junctions, tight junctions and gap junctions and to the VSMCs through myoendothelial gap junctions. The adherens and tight junctions form cell to cell zipper-like adhesion complexes [7]. Vascular endothelial cadherin (VE-cadherin) is the major structural protein of adherens junctions [8]. VE-cadherin binds β-catenin, which in turn binds to α-catenin, an actin binding protein, which connects the adherens junctions to the actin cytoskeleton. Disruption of VE-cadherin to β-catenin binding inhibits proper adherens junction assembly, resulting in decreased cell–cell adhesion and barrier disruption [8]. Further stabilization of adherens junctions is mediated by the binding of α-catenin to α-actinin and vinculin. The important role of VE-cadherin in promoting endothelial integrity was demonstrated in a mouse model in which intravenous injection of anti-VE-cadherin antibodies increased pulmonary vascular permeability [8]. Tight junctions are also present between adjacent endothelial cells and they not only restrict the movement of molecules between endothelial cells to the sub-endothelial space, but they also prevent diffusion of plasma membrane proteins between the apical and basolateral compartments [7]. The binding of occludins, claudins, and junctional adhesion molecules with zona occludens proteins connects the tight junctions with the actin cytoskeleton, again promoting barrier integrity [9].

Gap junctions form conduits between adjacent cells allowing direct intercellular communication [10,11]. Six connexin subunits oligomerize to form a hemichannel in the plasma membrane, which can dock to another hemichannel in the plasma membrane of an adjacent cell, assembling a complete gap junction channel [11]. These gap junctions allow intercellular transport of small molecules including Ca^{2+} and cyclic nucleotides. Gap junctions formed by connexin 43 have been recently been linked to pregnancy adaptations involving $[Ca^{2+}]i$ signaling [10]. Activation of phosphorylated eNOS and subsequent production of NO to induce vasodilation, an essential vascular adaptation in pregnancy, depends on increased $[Ca^{2+}]i$ [12]. Both NO and prostacyclin increase cAMP/cGMP production, which in turn increases connexin 43 expression and gap junctions. Using freshly isolated uterine artery endothelial cells from a pregnant sheep, Bird et al. showed increased connexins 37 and 43 that correlated with increased eNOS expression [10]. Connexins, therefore, play an important role in regulating vascular tone through Ca^{2+}-mediated eNOS activation during pregnancy, but whether connexins are dysfunctional in complicated pregnancies such as preeclampsia, is currently under investigation [10]. However, Krupp et al. have recently shown in umbilical vein endothelium isolated from pregnancies complicated by preeclampsia that reduced NO was accompanied by a failure of sustained Ca^{2+} bursting [13].

In addition to the gap junctions between endothelial cells, myoendothelial gap junctions connect the endothelial cells to the underlying VSMCs [10]. The formation of these myoendothelial gap junctions is inversely correlated with arterial diameter and the number of VSMCs [14]. These junctions could, therefore, play important physiological roles in smaller resistance vessels. Myoendothelial gap junctions also play a role in vascular tone regulation and may be important for vascular adaptations in pregnancy [10,15].

3. Regulation of endothelial barrier function

Barrier integrity is regulated by both circulating and endothelial-derived factors. The effectiveness of the barrier differs depending on the vascular bed; for example, it is greater in cerebral compared to mesenteric vasculature. One of the most studied signaling systems that maintains endothelial barrier integrity is angiopoietin-1, which signals through Tie2 to enhance endothelial barrier function by regulating the stress fiber formation [16]. In contrast, disruption of endothelial barrier function is common in vascular disorders mediated by inflammatory cytokines such as VEGF, thrombin, TNF-α, IL-6, ICAM-1 and VCAM-1 [8,9]. Vascular inflammation is an important component of hypertension and cardiovascular disease. In pregnancy, inflammation contributes to preeclampsia and intrauterine growth restriction (IUGR) [17]. Detailed mechanisms of cytokine-induced disruption of the endothelial barrier have been described [7]. However, the contributions of changes in endothelial permeability to regulation of vascular tone in non-pregnant or pregnant conditions remain to be elucidated.

Factors that can both enhance and decrease the endothelial barrier include S1P and NO. The opposing functions of S1P depend