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Review

Flow (shear stress)-mediated remodeling of resistance arteries in diabetes

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ABSTRACT

Shear stress due to blood flow is the most important force stimulating vascular endothelium. Acute stimulation of the endothelium by shear stress induces a vasodilatation mainly due to the release of nitric oxide (NO) among other relaxing agents. After a chronic increase in blood flow (shear stress), the endothelium triggers diameter enlargement, medial hypertrophy and improvement of arterial contractility and endothelium-mediated dilation. Shear stress-mediated outward remodeling requires an initial inflammatory response followed by the production of reactive oxygen species (ROS) and peroxinitrite anions, which activate MMPs and extracellular matrix digestion allowing diameter expansion. This outward remodeling occurs in collateral growth following occlusion of a large artery. In diabetes, an excessive ROS production is associated with the formation of advanced glycation end-products (AGEs) and the glycation of enzymes involved in vascular tone. The balance between inflammation, AGEs and ROS level determines the ability of resistance arteries to develop outward remodeling whereas AGEs and ROS contribute to decrease endothelium-mediated dilation in remodeled vessels. This review explores the interaction between ROS, AGEs and the endothelium in shear stress-mediated outward remodeling of resistance arteries in diabetes. Restoring or maintaining this remodeling is essential for an efficient blood flow in distal organs.

Contents

1. Introduction

The endothelium plays a central role in vascular homeostasis and allows the vasculature to adapt to the local need of each tissue. In response to various stimuli, the endothelium produces nitric oxide (NO) from the amino acid L-arginine that induces the relaxation of the muscular layer and vascular dilation. In resistance arteries, the endothelium produces vasodilator agents such as prostacyclin and EDHF as well as vasoconstrictor agents such as angiotensin II, thromboxan A_2 (TxA_2) and endothelin-1. Pulsatile blood flow produces three types of hemodynamic forces: a) hydrostatic pressure generated by the liquid, aa) cyclic stretching and aaa) shear stress. Stretching is a cyclic distension of the wall caused by a transmural pressure gradient and depends on thickness of the vessel wall, its composition and the degree of contraction of smooth muscle. The main effect of cyclic stretching is the induction of oxidative stress in endothelial cells. On the other hand, shear stress results from the frictional forces exerted by blood flow directly on endothelial cells and is determined by blood flow,

Abbreviations: EDHF, endothelium-derived hyperpolarizing factor; FMD, flow-mediated dilation; NO, nitric oxide; ROS, reactive oxygen species; ONOO-, peroxinitrite anion; eNOS, endothelial NO-synthase; FMD, flow-mediated dilation; MMPs, metallo-proteases; ECM, extracellular matrix; AT1/2R, angiotensin II type 1 or 2 receptor.

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blood viscosity and vessel diameter. Acute changes in blood flow or shear stress induce immediate changes in tone by activating endothelial cells, which produce vasoactive agents. In response to a chronic change in flow, the endothelium induces deeper changes in arterial wall structure and function usually referred as remodeling.

Diabetes is increasing worldwide in industrialized as well as in developing countries, posing a major challenge to global human health. Cardiovascular diseases are the major cause of morbidity and mortality in type 2 diabetes due to arterial structure and functional alteration. The most important damages observed in diabetic patients are hind limb ischemia and end organ damages (Schaper et al., 2000). Vascular damages associated with diabetes could be explained in part by the reduction of small resistance arteries capacity to adapt in response to chronic changes in blood flow. Indeed, shear stress-mediated remodeling of small resistance arteries is essential for collateral growth following arterial occlusion and for revascularization of ischemic tissues, a key problem in diabetes (Fig. 1).

This article focuses on the role of the endothelium in flow-mediated remodeling of resistance arteries and on the changes induced by metabolic syndrome and diabetes. Indeed, local blood flow supply is a critical issue in metabolic disorders associated with overweight and/or diabetes.

2. Control of microvascular tone and role of shear stress

The vasculature consists of large arteries branching out into smaller and smaller vessels terminated by capillaries. Capillaries irrigate tissues and are connected to larger veins via venules. Structural and functional differences between large arteries and arterioles are obvious when comparing the aorta to pre-capillary arterioles. Indeed, differences in blood pressure, pulsatility, and organ or tissue specificity induce a specialization of vascular cells. Changes in the hemodynamic environment induce short-term responses and structural adaptation of the vascular tree, thus allowing an optimal tissue perfusion (Bevan and Siegel, 1991; Bevan and Henrion, 1994). Small arteries having the most important influence on local blood flow are called resistance arteries. These arteries are submitted to chemical and neuro-hormonal influences in addition to the continuous effect of the mechanical factors generated by the blood stream, mainly pressure and flow. Pressure induces a rapid and sustained vasoconstriction called myogenic tone (Henrion, 2005; Prewitt et al., 2002; Hill et al., 2006). Myogenic tone represents a tonic arteriolar contraction facilitating the action of the other vasoactive systems, mainly the sympathetic and the renin–angiotensin systems, through a synergistic mechanism or potentiation, controlling the sensitivity to calcium of the contractile apparatus (Henrion et al., 1992a, 1992b; Dowell et al., 1996a, 1996b; Iglarz et al., 1998; Yeon et al., 2002). This potentiation relies mainly on the activation of the RhoA-Rho-kinase pathway (Dubroca et al., 2007) leading to a higher level of filamentous actin in the cytosol (Cipolla et al., 2002). On the other hand, blood flow produces shear stress, which stimulates the endoluminal surface of the endothelium. Flow (shear stress)-mediated dilation (FMD) represents a basal vasodilator stimulus activating continuously the endothelium. Together with myogenic tone, FMD determines a basal tone over which other vasoactive systems may act more efficiently. Shear stress induces the production of nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) as well as the production of vasoconstrictor agents such as endothelin-1 and angiotensin II (Matrougui et al., 2000). A reduction in FMD is the hallmark of endothelial dysfunction and it is becoming more and more important in the detection, the follow-up and even the prevention of vascular disorders in a growing number of diseases described in recent review articles (Feletou and Vanhoutte, 2006; Aird, 2007a, 2007b). As shown in a recent review article (Yamamoto and Ando, 2011), a change in flow (shear stress) induces a complex response of the endothelial cell with the involvement of the extracellular matrix, the primary cilia and membrane-associated proteins, mainly ionic channels and adhesion molecules. The signal may also be transmitted to surrounding cells through the cytoskeleton and the integrins. Each may be affected by diabetes, especially in response to chronic changes in flow. Acute responses to flow seem to be rather affected by the excessive oxidative stress occurring in diabetes leading to reduced NO bioavailability (Fig. 2).

To assess the endothelial dysfunction in patients, a flow-mediated dilation method can be carried out noninvasively with ultrasonography

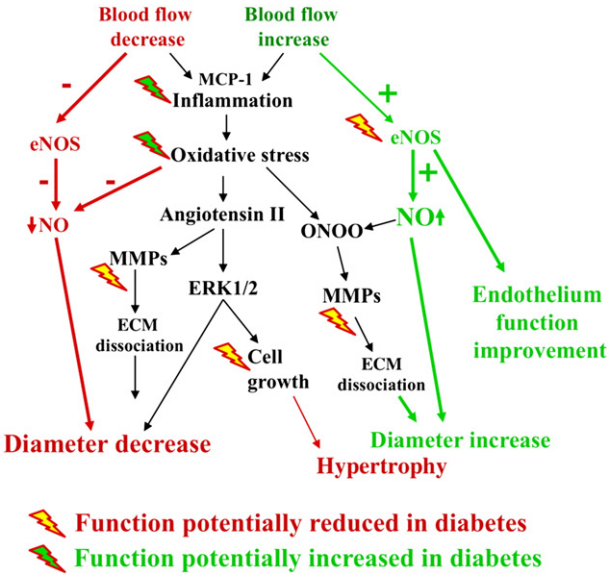

Fig. 1. Changes in blood flow, decreases or increases, induce an inflammatory response responsible for oxidative stress and synthesis of angiotensin II. This results in activation of metalloproteases (MMPs) that cause a partial dissociation of the extracellular matrix (ECM). The next step depends on the basal stimulus inducing the remodeling. In arteries subjected to increased flow, the endothelium is over-stimulated and produced more NO, which increases arterial diameter. In arteries subjected to low flow, the endothelium is under-stimulated and produces less NO. Thus NO counteracts less angiotensin II that can then contract the artery. In all cases, the remodeling is stabilized when the diameter reaches a level allowing normalization of shear stress. In the artery submitted to high-flow, activation of angiotensin II type 1 receptor and MAP kinase ERK1/2 induces a compensatory hypertrophy.