World Journal of Cardiology

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DOI: 10.4330/wjc.v7.i11.719

World J Cardiol 2015 November 26; 7(11): 719-741
ISSN 1949-8462 (online)

REVIEW

Vascular endothelial dysfunction and pharmacological treatment

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Author contributions: Su JB wrote the paper.

Conflict-of-interest statement: None declared.

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Received: May 5, 2015
Peer-review started: May 8, 2015
First decision: June 3, 2015
Revised: June 23, 2015
Accepted: September 16, 2015
Article in press: September 18, 2015
Published online: November 26, 2015

Abstract

The endothelium exerts multiple actions involving regulation of vascular permeability and tone, coagulation and fibrinolysis, inflammatory and immunological reactions and cell growth. Alterations of one or more such actions may cause vascular endothelial dysfunction. Different risk factors such as hypercholesterolemia, homocystinemia, hyperglycemia, hypertension, smoking, inflammation, and aging contribute to the development of endothelial dysfunction. Mechanisms underlying endothelial dysfunction are multiple, including impaired endothelium-derived vasodilators, enhanced endothelium-derived vasoconstrictors, over production of reactive oxygen species and reactive nitrogen species, activation of inflammatory and immune reactions, and imbalance of coagulation and fibrinolysis. Endothelial dysfunction occurs in many cardiovascular diseases, which involves different mechanisms, depending on specific risk factors affecting the disease. Among these mechanisms, a reduction in nitric oxide (NO) bioavailability plays a central role in the development of endothelial dysfunction because NO exerts diverse physiological actions, including vasodilation, anti-inflammation, antiplatelet, antiproliferation and antimigration. Experimental and clinical studies have demonstrated that a variety of currently used or investigational drugs, such as angiotensin-converting enzyme inhibitors, angiotensin AT1 receptors blockers, angiotensin-(1-7), antioxidants, beta-blockers, calcium channel blockers, endothelial NO synthase enhancers, phosphodiesterase 5 inhibitors, sphingosine-1-phosphate and statins, exert endothelial protective effects. Due to the difference in mechanisms of action, these drugs need to be used according to specific mechanisms underlying endothelial dysfunction of the disease.

Key words: Endothelial dysfunction; Endothelium-dependent vasodilation; Endothelial nitric oxide synthase; Inflammation; Nitric oxide; Pharmacological treatment; Reactive nitrogen species; Reactive oxygen species; Risk factors

Core tip: The endothelium is involved in the regulation of vascular tone and permeability, coagulation and fibrinolysis, inflammatory and immunological reactions

and cell growth. Cardiovascular risk factors cause vascular endothelial dysfunction through impairing endothelium-derived vasodilators, enhancing endothelium-derived vasoconstrictors, producing reactive oxygen species and reactive nitrogen species, activating inflammatory and immune reactions and promoting thrombosis. Among these mechanisms, a reduction in nitric oxide bioavailability plays a central role in the development and progression of endothelial dysfunction. A variety of currently used or investigational drugs exert endothelial protective effects according to specific mechanisms underlying endothelial dysfunction of the disease.

Su JB. Vascular endothelial dysfunction and pharmacological treatment. *World J Cardiol* 2015; 7(11): 719-741 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i11/719.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i11.719

INTRODUCTION

The endothelium is formed by a monolayer of endothelial cells. It constitutes a physical barrier between blood and tissues and regulates the exchange of molecules between blood and tissues. In addition, endothelial cells metabolize, synthesize and release a variety of substances, including vasoactive substances regulating vascular tone, blood pressure and local blood flow, the substances participating in coagulation, fibrinolysis and inflammatory and immunological reactions, reactive oxygen species (ROS) and reactive nitrogen species (RNS) involved in oxidation and nitrosylation of proteins and lipids, and growth factors promoting cell growth (Table 1). Any perturbation affecting the capacity and equilibrium of the endothelium as a physical barrier and to metabolize, synthesize and release these substances will cause endothelial dysfunction, which contributes to the development and progression of cardiovascular diseases. After summarizing the role of a number of endothelium-derived vasoactive substances and risk factors of endothelial dysfunction, this review focus on several categories of pharmacological substances that may be used for improving endothelial function.

Table 1 Some of endothelium-derived substances

Vasoactive substances
Endothelium-derived vasodilators
Adrenomedullin
Endothelium-derived hyperpolarizing factors
Kinins
Nitric oxide
Prostacyclin
Endothelium-derived vasoconstrictors
Angiotensin II
Endothelin-1
Vasoconstrictor prostanoids
Coagulation and fibrinolysis
Coagulation
Factor V
Heparan sulfate
Protein C
Protein S
Thrombomodulin
Tissue factor
von Willebrand factor
Fibrinolysis
Plasminogen activator inhibitor
Tissue plasminogen activator
Urokinase
Growth factors
Basic fibroblast growth factor
Insulin-like growth factor
Platelet-derived growth factor
Transforming growth factor
Inflammatory and immunological mediators
Cytokines
Interleukins
Monocyte chemoattractant protein 1
Transforming growth factor
Tumor necrosis factor-α
Adhesion molecules
Intercellular adhesion molecules
Platelet-endothelial cell adhesion molecules
Selectins
Vascular cell adhesion molecules
Reactive oxygen species and reactive nitrogen species
Reactive oxygen species
Hydrogen peroxide (H_2O_2)
Hydroperoxyl (HO_2)
Superoxide (O_2^-)
Reactive nitrogen species
Nitrite (NO_2^-)
Nitrogen dioxide (NO_2)
Peroxynitrite ($ONOO^-$)
Nitryl chloride (NO_2Cl)

ENDOTHELIUM-DERIVED VASOACTIVE SUBSTANCES

The endothelium releases a variety of vasoactive substances, including different vasodilators such as nitric oxide (NO), prostacyclin, kinins, and endothelium-derived hyperpolarizing factors (EDHF), vasoconstrictors such as endothelin-1 and PGH_2, and ROS. Among endothelium-derived vasodilators, NO occupies a central position because changes in the release of endothelial NO play a crucial role in the perturbation of vascular homeostasis and in the development of endothelial dysfunction associated with various cardiovascular disorders.

NO

NO is synthesized from the amino acid L-arginine by a family of enzymes, the NO synthase (NOS), through the L-arginine-NO pathway. Three isoforms of NOS have been identified. Neuronal NOS (nNOS), initially found in the nervous system, is also constitutively expressed in skeletal and cardiac muscles, vessels and many other tissues. Endothelial NOS (eNOS) is constitutively expressed mainly in endothelial cells, whereas the expression of inducible NOS (iNOS) can

be stimulated by diverse factors such as cytokines and endotoxin in different circumstances. The endothelium-derived NO release is primarily ensured by eNOS and complemented by nNOS expressed in vascular endothelial cells. Therefore, eNOS is primordial in the regulation of NO production by endothelial cells. The activity of eNOS depends on several factors, including eNOS mRNA and protein expression, the abundance of asymmetric dimethylarginine (ADMA, an endogenous eNOS inhibitor that competes with L-arginine for binding to eNOS)[1,2], the quantity and quality of cofactors such as tetrahydrobiopterin (BH4) and NADPH that are necessary for eNOS catalyzing NO production from L-arginine[3,4], its interaction with caveolin and heat shock protein 90 (hsp90)[5,6], and its translational modifications such as phosphorylation at different sites by multiple kinases or phosphatases [for example, phosphorylation at ser-1179 by phosphotidylinositol-3-kinase (PI3K)/protein kinase B (Akt) activates eNOS to initiate NO synthesis][7,8] and S-nitrosylation at cysteine residues[9]. In addition, excessive superoxide (O_2^-) and hydrogen peroxide (H_2O_2) production due to increased NAD(P)H oxidase[10,11] and eNOS uncoupling induced by changes in oxidized low density lipoprotein (OxLDL), caveolin-1, BH4, a switch from S-nitrosylation to S-glutathionylation and oxidation of the zinc-thiolate complex by peroxynitrite ($ONOO^-$) also affects effective eNOS activity[12-15].

NO released by eNOS participates in the regulation of vascular tone. NO activates soluble guanylate cyclase by binding to its ferrous heme, leading to the conversion of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP) that causes vascular smooth muscle relaxation. Moreover, NO exerts antiinflammatory, antiplatelet, antiproliferative and antimigration actions that contribute to the maintenance of an adequate environment for the endothelium. Lacking eNOS gene in mice induces insulin resistance, hyperlipidemia and hypertension[16]. NO released by nNOS also participates in the regulation of vascular tone, especially for the regulation of vascular tone in skeletal muscles. Altered nNOS activity and protein levels contribute to muscular damage due to sustained vasoconstriction in patients with Duchenne muscular dystrophy[17,18] and endothelial dysfunction in dogs with Duchenne muscular dystrophy[19].

Prostacyclin

Prostacyclin (also called PGI2) is generated from arachidonic acid by cyclooxygenase (COX) in endothelial cells. Activation of IP receptors by PGI2 activates adenylate cyclase to synthesize cyclic adenosine monophosphate (cAMP) from adenosine triphosphate, causing vascular smooth muscle relaxation. However, PGI2 synthesis can be inactivated by increased cytokines[20] and under certain conditions, PGI2 exerts vasoconstrictor action and contributes to endothelial dysfunction[21].

EDHF

The term "EDHF" describes a set of substances causing vascular myocyte hyperpolarization and spreading endothelial hyperpolarization to vascular myocytes, resulting in vascular myocyte relaxation, which is not affected by blocking NO or prostacyclin production[22]. Interestingly, in eNOS/COX-1 double-knockout mice, EDHF-mediated vasodilation plays a compensatory role for the absence of endothelial NO[23]. EDHF hyperpolarize myocyte membranes by opening calcium-activated potassium channels named as BKca, IKca, and SKca according to their conductance (big, intermediate, and small conductance), leading to K^+ efflux[24-26]. EDHF-mediated vasodilation also involves epoxyeicosatrienoic acids (EETs), gap junction, reactive oxygen species and hydrogen peroxide, depending on the vascular beds and vessel types[24,25,27]. Cytochrome P450 epoxygenase catalyzes the production of EETs from arachidonic acid in different vessels and EETs participate in, at least partly, the hyperpolarization and relaxation of myocytes in these vessels[28,29]. It is worth noting that EDHF-mediated vasodilation is a complex phenomenon, which involves multiple signaling pathways that may be not exclusive in response to different stimuli[24-26]. Altered EDHF signalings may account for endothelial dysfunction in some cardiovascular disorders as suggested by studies in animals. For example, a defect in connexins that compose gap junctions is partly responsible for impaired vasodilator responses in hypertensive rats[30] and in diabetic rats[31]. However, the role of EDHF in endothelial dysfunction in human cardiovascular diseases remains elusive. This may be related to the difficulty that the function of EDHF can only be deciphered after impairment of NO and prostacyclin-mediated responses.

Kinins

Kinins such as bradykinin can be generated in vessel walls, especially in endothelial cells that contain the components such as kinin precursors and kinin-generating enzymes, necessary for the production of kinins[32]. The biological effects of kinins are mediated by stimulation of constitutively expressed B2 receptors and inducible B1 receptors. In endothelial cells, activation of B2 receptors by bradykinin releases NO, prostacyclin, EDHF and tissue plasminogen activator, which exert diverse physiological and pathological actions on cardiovascular system, including regulation of coronary vascular tone and local blood flow of organs, coagulation, fibrinolysis, and water-electrolyte[33,34]. Stimulation of B1 receptors by its agonists also induce NO-mediated vasodilation[35]. Due to very short half-life in the blood, bradykinin essentially plays an autocrine/paracrine role. Experimental studies have demonstrated a protective role of bradykinin B2 receptors on cardiovascular function. It is, at least in part, due to opposing effects of bradykinin B2 receptor activation on angiotensin Ⅱ AT1 receptor activation because of multiple cross-talks between the kallikrein-kinin system and the renin-

angiotensin system[36]. This explains the contribution of kinins to the cardiovascular protective effects of angiotensin-converting (ACE) inhibitors and angiotensin AT1 receptor blockers. Deletion of both B1 and B2 receptors in diabetic mice exacerbates nephropathy as indicated by increased oxidative stress, mitochondrial DNA deletions and renal expression of fibrogenic genes, suggesting a protective role of the kallikrein-kinin system on diabetic nephropathy[37]. However, these mice exhibit neither accelerated cardiac dysfunction nor ROS production, challenging the protective role of kinins in this setting[38]. Otherwise, kinins can increase endothelial permeability[39] and are involved in inflammatory responses by activating phospholipase A2 to release arachidonic acid that is used for the production of vasoconstrictor prostanoids, which may be harmful for endothelial function.

Adrenomedullin

Adrenomedullin (AM), a vasodilator peptide initially identified from human pheochromocytoma, can be secreted by vascular cells, especially by endothelial cells[40-42]. AM exerts its action in the cardiovascular system through receptor complexes composed of the calcitonin receptor-like receptor and receptor activity-modifying proteins. In vessels, the receptors for AM are expressed in both endothelial and smooth muscle cells[43,44]. AM-induces endothelium-dependent and -independent vasodilation, depending upon species and vascular beds[42]. AM-induced endothelium-dependent vasodilation is mediated by PI3K/Art/NO/cGMP pathway, the activation of cGMP-stimulated protein kinase G and/or the production of a vasodilator prostanoid (likely prostacyclin)[42,45,46], whereas AM-induced endothelium-independent vasodilation involves the opening of K^+ channels (calcium-activated K^+ channels or ATP sensitive K^+ channels, probably depending upon vascular beds) and the activation of cAMP-dependent protein kinase A[42,47]. In addition to vasodilator effect, AM was shown to inhibit angiotensin II-induced ROS generation by NAPDH[48], and AM -deficient mice developed insulin resistance due to increased ROS[49]. AM protects bone marrow-derived mononuclear cell and endothelial progenitor cells from apoptosis and exerts a vascular protective role[50,51]. AM also exerts an protective effect on endothelial barrier function and reduces endothelial permeability in response to inflammation and endotoxin[52-56]. Otherwise, AM posses angiogenesis property and participates in vascular remodeling [50,57,58]. Plasma AM levels were shown to be higher in many pathological situations such as arteriosclerosis, sepsis, essential or pulmonary hypertension and heart failure[52,59-63], whereas intracoronary AM levels were lower in patients with stable coronary disease[64] and in infants with brain damage after surgery under cardiopulmonary bypass[65]. Increased AM levels were interpreted as a compensatory mechanism to protect cardiac and vascular function[61,66]. Expression of receptors for AM was shown to be increased in rats with heart failure though its signification remains elusive[67,68]. Despite its protective role in the cardiovascular system, AM was shown to be involved in the growth of different tumors such as prostate, colorectal and bladder tumors, and AM and its receptors are potential targets for the treatment of these tumors[69-71].

Angiotensin Ⅱ

Endothelial cells express ACE and angiotensin AT1 and AT2 receptors. Once released, angiotensin Ⅱ immediately binds to these receptors and those expressed on smooth muscle cells. Although angiotensin Ⅱ causes both vasoconstriction *via* AT1 receptors and vasorelaxation by stimulating AT2 receptors, angiotensin Ⅱ-induced vasoconstriction is predominant in many circumstances. Moreover, angiotensin Ⅱ exerts multiple actions affecting endothelial function. Angiotensin Ⅱ upregulates endothelial receptors for OxLDL, stimulates OxLDL uptake, and enhances OxLDL-mediated ROS generation and endothelial cell apoptosis[72]. Angiotensin II increases receptors for vascular endothelial growth factors and matrix metalloproteinases (MMPs), which may account for increases in endothelial permeability and vascular remodeling[73-75]. Angiotensin Ⅱ increases the expression of plasminogen activator inhibitor type 1 (a natural inhibitor of tissue-type plasminogen activator and urokinase-type plasminogen activator) in endothelial cells[76], thereby favoring thrombosis. Angiotensin II favors inflammation by inducing COX-2 expression[74] and increasing cytokine tumor necrosis factor-alpha (TNF-α)[75]. Although angiotensin Ⅱ can upregulate eNOS and inducible NO synthase (iNOS) expression, it reduces eNOS-derived NO by promoting eNOS uncoupling through monocyte-dependent S-glutathionylation[77]. In addition, the activation of AT2 receptors also contributes to the angiotensin Ⅱ-induced vascular remodeling[78]. These actions of angiotensin Ⅱ may contribute to endothelial dysfunction as the renin-angiotensin system is activated, as is the case in atherosclerosis[79] and heart failure.

Endothelin-1

Although endothelin-1 can upregulate eNOS expression by enhancing eNOS mRNA stability *via* protein tyrosine kinases and protein kinase C-dependent pathways[80,81], endothelin-1 *via* type A endothelin receptors induces expression of adhesion molecules and neutrophil adhesion to endothelial cells, and promotes cytokine and ROS generation[82-84]. Elevated endothelin-1 blood levels can be seen in atherosclerosis[85], pulmonary hypertension[86] and heart failure[87,88], which may account for the development of endothelial dysfunction under these circumstances. Although the activation of Type B endothelin receptors generally induces vasodilation, these receptors appear to mediate endothelin-1-induced ROS production and contribute to endothelial dysfunction in obese rats[82].

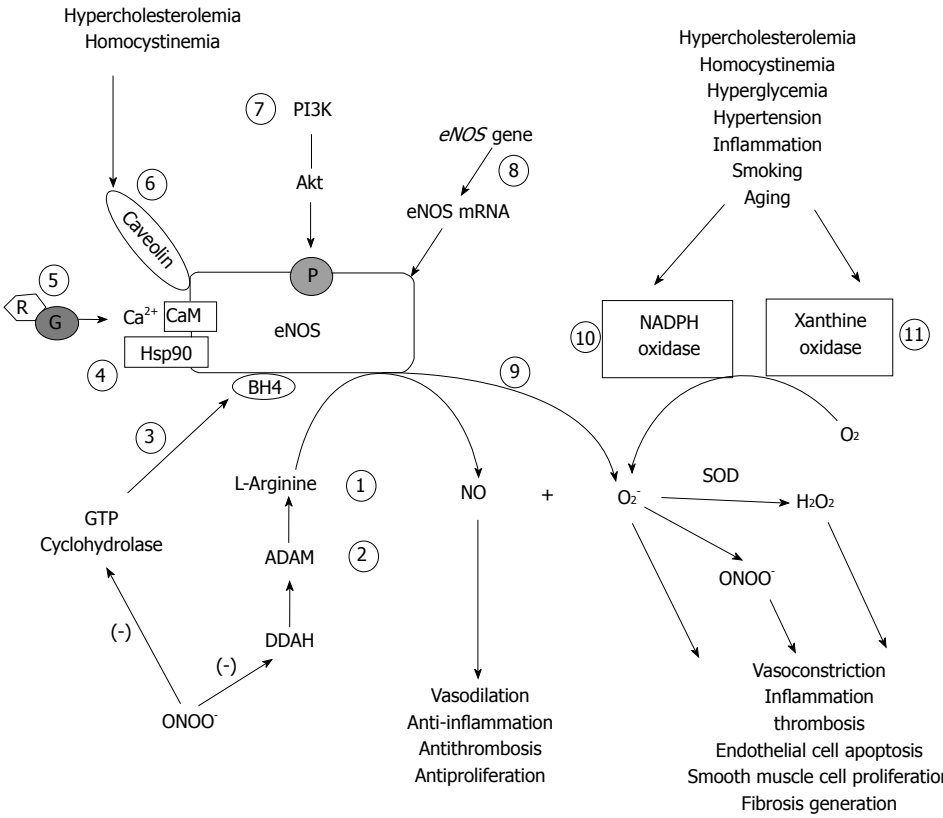

Figure 1 Mechanisms underlying the reduction in nitric oxide bioavailability involve both reduced nitric oxide production and increased nitric oxide scavenging. A reduction in NO production can be resulted from: (1) decreased L-arginine availability due to L-arginine deficiency and/or changes in L-arginine transporter; (2) accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of endothelial NO synthase (eNOS); (3) deficiency or modification of cofactor tetrahydrobiopterin (BH4); (4) altered interactions between eNOS and caveolin due to increased caveolin-1; (5) changes in receptor-coupled G proteins; (6) altered eNOS-heat shock protein 90 (Hsp90) interaction due to changes in Hsp90 abundance; (7) changes in calcium-independent phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)-mediated eNOS activation by tyrosine or serine phosphorylation; and (8) decreased eNOS expression due to reduced eNOS gene transcription and/or decreased eNOS mRNA stability. Increased NO scavenging by reactive oxygen species (ROS) and reactive nitrogen species (RNS) can be due to: (9) eNOS uncoupling related to changes in BH4, caveolin-1 and oxidized low density lipoproteins; (10) increased NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) expression and activity; and (11) increased xanthine oxidase expression and activity. CaM: Calmodulin; DDAH: Dimethylarginine dimethylaminohydrolase; SOD: Superoxide dismutase; NO: Nitric oxide.

Vasoconstrictor prostanoids

Endothelial cells can produce vasoconstrictor prostaglandin H2 (PGH2), thromboxane A2 (TXA2) and PGF2α. The production of these prostanoids is enhanced in hypertension, hypercholesterolemia, diabetes and vitamin E deficiency[89], which in turn upregulates NAPDH oxidase and type 4 and type 5 phosphodiesterases (PDE4 and PDE5)[90,91], resulting in increases in ROS production, cAMP and cGMP degradation, and vasoconstriction. TXA2 is also a potent activator of platelets, while activated platelets in turn release a large amount of TXA2 to promote thrombosis. Furthermore, TXA2 interacts with EDHF by inhibiting potassium channels, EETs and gap junction-mediated signaling pathways[27], which could account for the development of endothelial dysfunction.

RISK FACTORS CAUSING ENDOTHELIAL DYSFUNCTION

Clinically, endothelial dysfunction is characterized by impaired endothelium-dependent vasorelaxation in response to endothelium-dependent agonists such as acetylcholine and bradykinin, or to maneuvers that increase shear stress such as flow-mediated dilatation. Although mechanisms leading to endothelial dysfunction are multiple, a reduction in NO bioavailability is largely observed in many cardiovascular disorders. As shown in Figure 1, reduced NO bioavailability can be the consequence of decreased L-arginine availability[92], increased ADMA[1,2], altered interaction with hsp90[93] and phosphorylation of eNOS[94], as well as increased NO scavenging by excessive ROS generated by NADPH and xanthine oxidases[10,11,95] and eNOS uncoupling. It is worth noting that changes in caveolin-1[96], BH4[97], S-glutathionylation of eNOS[15,98] and OxLDL[12] are all involved in eNOS uncoupling. Importantly, a reduction in eNOS protein expression also leads to impaired eNOS activity and NO production, which can be observed in different cardiovascular diseases such as atherosclerosis, acute myocardial infarction and heart failure in animals and in humans[99-103]. However, mechanisms underlying endothelial dysfunction in different cardiovascular

disorders may be different, depending on risk factors contributing to the development of specific disease.

Hypercholesterolemia/atherosclerosis

Atherosclerosis is a chronic arterial disease involving the formation of multiple atheromatous plaques within arteries by accumulation of lipids due to the inability to remove LDL from macrophages. In this process, endothelial dysfunction related to hypercholesterolemia plays a pivotal role in the development of atherosclerosis. Hypercholesterolemia induces endothelial cell activation, leukocyte recruitment and adherence, platelet activation and adhesion within the vasculature, reflecting an inflammatory response and high thrombotic state that may cause endothelial dysfunction. Hypercholesterolemia increases superoxide and hydrogen peroxide production by increasing NAD(P)H oxidases[79], xanthine oxidase[95], and myeloperoxidase[104]. Increased superoxide reacts with NO, resulting in the formation of RNS and reduced eNOS-derived NO bioavailability. ROS induce oxidation of lipids, proteins and DNA, which cause cell damage, necrosis and cell apoptosis. Increased RNS induce nitrosylation reactions that modify the structure and function of proteins. Hypercholesterolemia increases caveolin-1 levels[105], also contributing to impaired eNOS activity. In addition, hypercholesterolemia disturbs reactions between oxygen radicals or enzymatic oxidation and lipoproteins, particularly LDL phospholipids and results in the production of oxidized phospholipids. These phospholipids contain arachidonic acid and bind to their membrane receptors, resulting in their accumulation within the cellular membrane, immune and inflammatory responses and ROS generation, which in turn induces eNOS uncoupling that impairs endothelium-dependent vasodilation induced by endogenous vasodilator such as kinins but enhances the role of endogenous vasoconstrictors such as angiotensin Ⅱ and endothelin-1, and promote endothelial dysfunction[106,107]. Therefore, endogenous vasoactive substances such as NO, prostanoids, ROS, RNS, AM, angiotensin Ⅱ, endothelin-1 and other substances interact and reduced NO bioavailability due to eNOS uncoupling is a key event contributing to the development of endothelial dysfunction and ultimately atherosclerosis.

Hyperhomocysteinemia

Homocysteine is a non-protein α-amino acid synthesized from methionine. Hyperhomocysteinemia is observed in patients with coronary disease and is correlated with endothelial dysfunction[108]. Homocysteine causes endothelial dysfunction through NO inhibition, vasoconstrictor prostanoid production, EDHF inhibition[109,110], angiotensin AT1 receptor activation, and ROS generation[111]. Homocysteine reduces eNOS activity by increasing asymmetric dimethylarginine production[112] and eNOS uncoupling *via* decreasing intracellular do novel synthesis of BH4[97], leading to decreased NO bioavailability and increased ROS generation. Furthermore, homocysteine downregulates eNOS expression in human endothelial cells[113], and induces endothelial loss, vascular deendothelialization and increases platelet adherence and consumption in baboons[114]. Homocysteine also increases ROS generation by phosphorylating NAPDH oxidase[115], and/or by increasing ACE activity *via* ACE homocysteinylation to generate angiotensin Ⅱ that activates NAPDH oxidase[116].

Hyperglycemia/diabetes mellitus

Endothelial dysfunction is associated with both insulin-dependent and independent diabetes mellitus. In this setting, hyperglycemia increases ROS generation through activating protein kinase C-mediated NAD(P)H oxidases[117] and peroxynitrite-mediated eNOS uncoupling[118], which also leads to reduced NO bioavailability. In addition, hyperglycemia increases iNOS expression and iNOS-derived NO and peroxynitrite production, leading to increased ROS and RNS levels and pancreatic islet endothelial cell apoptosis[119]. Moreover, hyperglycemia promotes platelet aggregation by increasing expression and circulating levels of endothelial adhesion molecules through protein kinase C-NFκB signaling pathway[120-122], and increases endothelial apoptosis[123]. All of these effects of hyperglycemia contribute to endothelial dysfunction observed in diabetes mellitus. Otherwise, increased release of vasoconstrictors such as prostanoids and endothelin-1 through protein kinase C-mediated pathway in response to hyperinsulinemia and hyperglycemia appears to precede changes in vascular complication or NO production[124,125]. Changes in EDHF also contribute to endothelial dysfunction, especially in type 2 diabetes as suggested in rat models in which an impaired EDHF-mediated vasorelaxation was observed before marked alteration in NO-mediated responses[126-129]. Therefore, altered NO bioavailability in type 2 diabetes appears to be a relatively late event worsening endothelial dysfunction.

Hypertension

An impaired endothelium-dependent vasorelaxation has been observed in patients with essential hypertension[130] and in several animal models of hypertension. This is related to a lower production of endothelium-derived vasodilators and/or over production of vasoconstrictors. An increased endothelin-1 production also plays a role in endothelial function, especially in pulmonary hypertension as lung is an important metabolic organ of circulating peptides such as adrenomodullin and endothelin-1. In this regard, pulmonary endothelin-1 extraction affects the incremental resistance of pulmonary vascular bed in response to increased cardiac work[131] and plasma endothelin-1 levels are closely related to clinical worsening of patients with pulmonary hypertension[132]. An impaired NO and EDHF-mediated vasorelaxation linked to an increased ADMA that inhibit eNOS and downregulates SKca in

endothelial cells has been reported in hypertensive patients and in spontaneous hypertensive rats[133]. Interestingly, alterations in EDHF appears to occur before alterations in NO pathways in different rat models of hypertension[134]. An reduced vasodilator response to AM has been observed in hypertensive patients[45]. However, an increased eNOS expression is generally observed in animal models of hypertension associated with angiotensin Ⅱ. In this case, angiotensin Ⅱ-induced oxidative stress and increases in the production of vasoconstrictor prostanoids and cytokines may account for the development of endothelial dysfunction. Furthermore, a reduced NO bioavailability has been reported in some models of hypertension. This appears to be linked to reduced substrate availability due to L-arginine deficiency and changed L-arginine transport[92] and to eNOS uncoupling due to oxidation of BH4 and/or S-glutathionylation, leading to increased ROS production[4,15]. Thus, although altered NO bioavailability may not be an initial event to induce endothelial dysfunction, it participates in its progression in hypertensive subjects.

Smoking

Endothelial dysfunction is one of the primary damages induced by cigarette smoke. Circulating cigarette toxins such as free radicals and reactive glycation products can react with endothelial cells and cause vascular impairment[135]. Cigarette smoking induces inflammatory state as indicated by elevation of white blood cells, adhesion molecules and cytokines, and increases ROS production and lipid peroxidation[136-141]. These mechanisms may contribute to impaired endothelium-dependent vasodilation observed in active smokers, even at young healthy adult, and in passive smokers[142,143]. However, despite a reduced NO bioavailability, eNOS expression has been shown to be increased in different endothelial cells or decreased in platelets in response to cigarette smoke[144,145]. Cigarette smoke extracts inhibits eNOS activity of pulmonary arterial endothelial cells through modifying eNOS phosphorylation pattern, which cannot be protected by antioxidants such as vitamin E and C[146,147]. In this setting, decreased NO bioavailability is probably the consequence of decreased eNOS activity due to modified eNOS phosphorylation and uncoupling as well as NO scavenging by increased ROS.

Inflammation

Endothelial cells produce inflammatory and immune mediators (Table 1) and undergo morphological modifications in response to inflammatory stimuli. The inflammatory and immune mediators increase endothelial permeability and promote adhesion of leukocyte to endothelial cells and interactions between chemokine receptors on leukocyte and proteoglycans on endothelial cells, leading to leukocyte transendothelial migration to inflammation sites. Inflammation induced endothelial dysfunction is often associated with impaired NO bioavailability. For example, typhoid vaccination induced an inflammatory response as indicated by increased cytokines and oxidative stress as well as a decreased endothelium-dependent vasodilation that was partially restored by antioxidant vitamin C[148]. In patients with viral myocarditis, acetylcholine induced a coronary vasoconstriction rather vasodilation[149]. Similar responses were also observed in mice with virus-induced myocarditis, which was attributed to reduced eNOS activity and expression[150]. In some autoimmune diseases, anti-endothelial antibodies cause abnormal immune activation that activates endothelial cells to release adhesion molecules and cytokines, leading to inflammation, increased permeability of the endothelium, thrombosis and cell apoptosis[151-153], which are, at least in part, responsible for endothelial dysfunction in this setting. Patients with rheumatoid arthritis have increased levels of cytokines and ADMA and impaired flow-mediated dilation[154]. Similarly, increased arterial stiffness is closely correlated with ADMA blood levels in systemic lupus erythematosus patients[155]. The increase in ADMA levels may account for reduced NO bioavailability in these autoimmune diseases.

In some cases, an over production of NO occurs in response to inflammation. Septic shock associated with a severe infection and sepsis is characterized by a profound hypotension, widespread endothelial injury and activation, multiple organ failure and death. In this setting, toxic microbe products, including endotoxins (bacterial membrane lipopolysaccharides, LPS) of gram-negative bacteria and analogous molecules in the walls of gram-positive bacteria and fungi, dramatically activate mononuclear cells to release cytokines[156] that upregulate bradykinin B1 receptors[157,158], inducible NO synthase[159] and COX-2[160], which increase NO and prostaglandin E2. In this regard, blocking or deleting bradykinin B1 receptors might yield benefits for the treatment of septic shock. However, experimental studies showed conflicting results regarding the role of kinins in septic shock in animals. Mice with overexpression of B1 receptors exhibited an increased susceptibility to develop septic shock and mice lacking B1 receptors or both B1 and B2 receptors had an enhanced resistance to LPS-induced sepsis[161-163], whereas mice lacking B1 receptors had an higher mortality in response to LPS[164] and additional B1 receptor blockade suppressed the beneficial effect of B2 receptor blockade[165]. Similarly, B2 receptor blockade showed no effect or amelioration in porcine sepsis[165,166]. Results regarding the role of NO, particularly iNOS in septic shock are also elusive. Experiments in rats and in human blood cells showed that iNOS expression is correlated with cell apoptosis in septic shock[167,168]. Selective iNOS inhibition improved hemodynamics and mortality in nondiabetic rats with LPS-induced sepsis but not in diabetic rats[169], whereas depletion of iNOS resulted in increased dysfunctional mitochondria, IL-

1β production and caspase-1 activation in response to LPS in myeloid cells from both mice and humans and increased NLRP3 inflammasome-mediated cytokine production and mortality in mice with LPS-induced sepsis, which was prevented by NLRP3 deficiency[170]. Although treatment with methylene blue that has the ability to scavenge NO and to inhibit NO synthase showed a transient and reproducible beneficial effect on systemic vascular resistance, arterial pressure and organ function in patients with septic shock, but its effect on mortality remains unknown[171,172].

Aging

Aging is accompanied by complex structural and functional modifications of the vasculature, leading to dysfunction of both the endothelium and smooth muscle cells. Changes in aged smooth muscle cells are characterized by changed migration, proliferative and apoptotic behavior, increased response to vasoconstrictors and decreased expression of Ca^{2+}-activated K^+ channels in coronary arteries[173,174]. Aged endothelial cells are associated with decreased NO synthesis and sensitivity to agonist and mechanic stimuli that promote eNOS expression but increased sensitivity to be apoptotic[175,176]. Loss of PI3K/Akt-dependent eNOS phosphorylation seems to be a main mechanism explaining the reduction in NO production in old rats[94]. In addition, aging of endothelial cells is associated with increased production of vasoconstrictor prostanoids, endothelin-1 and ROS[176-178]. ROS are mainly produced by mitochondrial respiratory chain and NADPH oxidases, although eNOS uncoupling my also contribute to increased ROS during aging[179].

METHODS FOR MEASURING ENDOTHELIAL DYSFUNCTION

In animals, endothelial dysfunction can be measured by examining vasodilator responses to endothelium-dependent substances such as acetylcholine, bradykinin and serotonin in comparison with responses to endothelium-independent molecules such as NO donor in the absence and presence of NOS inhibitor and COX inhibitor *in vivo*[180,181] and in isolated vessels[19,182].

The methods used in clinical practice to measure endothelial dysfunction are detailed elsewhere[183]. This includes invasive methods by using quantitative angiography and intracoronary Doppler wire within coronary circulation and non-invasive methods, including venous occlusion plethysmography to measure forearm blood flow, flow-mediated dilatation in brachial artery, and peripheral arterial tonometry measuring pulsatile volume changes in the distal digit[183].

In addition, some circulating biomarkers such as endothelin-1, E-selectin, von Willebrand factor, thrombomodulin, intercellular adhesion molecules and vascular cell adhesion molecules can also be analyzed to detect endothelial dysfunction, although none of them are specific[183].

CARDIOVASCULAR DRUGS IMPROVING ENDOTHELIAL FUNCTION

Experimental and clinical studies have shown that numerous currently used or investigational drugs can improve endothelial function, although they have different structure and mechanisms of actions.

ACE inhibitors and AT1 blockers

Since the success of ACE inhibitors in the treatment of heart failure and discovery of their multiple actions, ACE inhibitors and AT1 blockers are widely used to the treatment of hypertension, arthrosclerosis, diabetes and some autoimmune diseases. It is well established that ACE inhibitors can improve endothelial function in animals with heart failure[184] and in patients with coronary artery disease[185,186]. This effect is related to both reduction in angiotensin Ⅱ and increase in bradykinin accumulation. In addition, ACE inhibitors upregulate eNOS expression in animals[102,187]. The effect of ACE inhibitors on eNOS expression is mediated by bradykinin B2 receptors, which can be blocked by B2 receptors blockers[102,187]. ACE inhibitors and AT1 blockers also inhibit ROS production and COX-2-derived vasoconstrictors, which contribute to endothelial protective effects of these drugs[188]. It appears that the combination of both ACE inhibitor and AT1 blocker does not produce more beneficial effects on endothelial dysfunction than monotherapy in a murine model of atheroclerosis[189], whereas the combination of a stain with an ACE inhibitor or an AT1 blocker produces additive effects on systemic inflammation biomarkers[190]. Also, the combination of ramilapril with felodipine, an calcium channel blocker does not induce more effect on endothelium-dependent vasodilation than each drug alone but increases endothelium-independent vasodilation in spontaneous hypertensive rats[191].

Antioxidant agents

Several substances having very different molecular structure and proprieties, such as vitamin C and E, N-acetylcysteine and genistein exert antioxidant effects through different mechanisms.

Vitamin C can improve endothelium-dependent response in circumstances such as chronic smoking, diabetes mellitus, hypercholesterolemia and hypertension[136,192-195]. Vitamin C protects the endothelium by scavenging superoxide, which in turn prevents NO scavenging, lipid peroxidation, platelet and neutrophil activation, and adhesion molecule upregulation[136,196]. Vitamin C scavenges peroxidase-generated reactive nitrogen species and inhibits myeloperoxidase/H_2O_2/nitrite-mediated LDL oxidation[197]. Vitamin E also exerts endothelial-protective effects in smoking and hypercholesterolemia[194,198] but its effects in diabetes remains controversial[199,200]. Vitamin E acts as a lipid

soluble antioxidant, scavenging hydroperoxyl radicals in lipid milieu[201].

N-acetylcysteine is a non-essential amino acid, essentially used in the treatment of cough. However, experimental studies have demonstrated that N-acetylcysteine is a potent antioxidant. It acts on the production of glutathione, which protects the cardiovascular system from harmful effects of TNF-α that induces glutathione depletion and ROS production *via* NADPH oxidase and ceramide[202-206]. For example, N-acetylcysteine improves coronary and peripheral vascular endothelium-dependent responses in patients with or without atherosclerosis[203]. The effect of N-acetylcysteine on endothelial dysfunction is associated with inhibition of NADPH oxidase expression, leukocyte adhesion and inflammatory cytokine secretion[204]. In addition, N-acetylcysteine inhibits von Willebrand factor dependent platelet aggregation and collagen binding in human plasma and in mice[207], attenuates MMPs expression in microvascular endothelial cells and in rats[202,208], and inhibits caveolin-1 upregulation and improves endothelial barrier function in mice[209], which may also contribute to the endothelial protective effect of N-acetylcysteine. N-acetylcysteine interacts with endogenous and exogeneous vasodilators. For example, in patients with systemic sclerosis, N-acetylcysteine induces vasodilation in association with a reduction in plasma AM concentrations[210] and potentiates hypotensive effects of ACE inhibitors in hypertensive patients[211].

Genistein is a soya-derived phytoestrogen and exerts an antioxidant effect. Genistein attenuates endothelial dysfunction in hypertensive rats and hyperhomocysteinemic rats. This endothelial protective effect appears to be due to increases in eNOS activity and expression and decreases in cytokine and ROS generation[212-215]. Genistein also improves endothelium-dependent vasodilator response in healthy postmenopausal women, increases plasma nitrite/nitrate concentration but decreases plasma endothelin-1 levels[216]. In this regard, genistein may be useful for the treatment of endothelial dysfunction associated with atherosclerosis and hypertension.

Beta blockers

Some beta blockers, particularly the β1-selective beta blockers exert endothelial protective effects. Nebivolol, a β1-antagonist with β2,3-agonist property, improves endothelium-dependent vasodilator responses in patients with essential hypertension[217,218] and in smokers[219]. Nebivolol also improves endothelial function, which is associated with reduced vascular remodeling and expression of endothelin-1 and cytokines in rats with pulmonary hypertension and in endothelial cells taken from these rats[220]. The effect of Nebivolol on endothelial function appears to be mediated by increasing NO release and reducing prothrombotic blood levels of fibrinogen, homocysteine and plasminogen activator inhibitor-1, especially in smokers[218,219]. Carvedilol, a non-selective β1- and β2 antagonist with α-antagonist property, also improves endothelium-dependent responses in patients with essential hypertension but this seems to be related to its antioxidant capacity[218]. The combination of carvedilol with an ACE inhibitor produces more beneficial effect on endothelial function than each drug alone in hypertensive patients with obesity[221]. Thus, this type of beta blockers and its combination are suitable for the treatment of endothelial dysfunction associated with hypertension, atherosclerosis, and probably diabetes.

Dihydropyridine calcium channel blockers

Nicardipine and nifedipine protect against ROS-induced endothelial cell death and lose of glutathione in cultured cells[222]. Benidipine exerts an endothelial protective effect against OxLDL induced ROX generation in human endothelial cells[223]. Israpidine improves endothelial function in cholesterol-fed rabbit[224]. Thus, the endothelial protective effect of dihydropyridine calcium channel blockers is mainly mediated by their antioxidant actions related to reduction in lipid peroxidation and associated ROS generation[222,225]. In addition, some dihydropyridines such as, amlodipine, azelnidipine and nifedipine were shown to exert an antiinflammatory action as indicated by decreased C-reactive protein and interleukin-6 levels as well as leucocyte activation[226,227]. Amlodipine or in combination with an renin inhibitor improves endothelial dysfunction in hypertensive patients, which seems to be linked to its NO-releasing action and anti-inflammatory effect[181,228-230]. In addition, the combination of amlodipine with a statin induces more favorable vascular effects than each drug alone in rats with hypertension or diabetes[231,232]. Thus, in addition to hypertension, dihydropyridines may also be useful for the treatment of endothelial dysfunction in diabetes.

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 (PDE5) is a cytosolic enzyme localized in vascular smooth muscle, heart, skeletal muscle, platelet, placenta, brain, kidney, liver, pancreas, gastrointestinal tissues and lung[233]. In vasculature, the primary action of PDE5 is to degrade cGMP and thereby induces vasoconstriction. PDE5 inhibitors are a class of drugs used to improve erectile dysfunction. These drugs block PDE5-induced cGMP degradation, leading to tissue cGMP accumulation and vasodilation[234]. PDE5 inhibitors upregulate eNOS expression and thereby increase NO release[235,236], which may contribute to long-term vasodilator effects of PDE5 inhibitors. PDE5 inhibitors also exert other initially unexpected effects. For example, in mouse hind limb ischemia model, treatment with sildenafil not only improves blood flow recovery but also increases capillary density and endothelial progenitor cell mobilization[237]. In patients with vasculogenic erectile dysfunction, daily treatment with vardenafil reduces both arterial stiffness and plasma AM level[238]. These effects may also account

for the effects of chronic PDE5 inhibition. In addition to erectile dysfunction, PDE5 inhibitors can improve endothelial dysfunction in other circumstances. For example, PDE5 inhibition improves coronary and peripheral vascular endothelial function, and inhibits platelet activation in patients with coronary artery disease[239] or with congestive heart failure[240-242], and improves endothelium-dependent vasorelaxation in rats with experimental diabetes mellitus[243]. PDE5 inhibitors also improves erectile function in patients with systemic sclerosis and reduces plasma endothelin-1 concentration[244]. Similarly, PDE5 inhibitors improve Raynaud's phenomenon characterized by reduced blood flow to fingers and toes in response to cold and stress, probably through decreasing plasma endothelin-1 and improving microcirculation[245]. However, the mechanism underlying endothelin-1-reducing effect of PDE5 inhibitors remains to be determined.

Statins

Statins, inhibitors of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase are a class of drugs utilized to reduce hypercholesterolemia, especially LDL cholesterol. In 1994, pravastatin was shown to improve endothelium-dependent response of coronary and peripheral arteries in patients with hypercholesterolemia[246], which was confirmed later by other studies[247]. The beneficial effect of statins on endothelial function involves multiple mechanisms. Statins improving endothelial dysfunction is partly due to their lowering LDL cholesterol effect, while native LDL and OxLDL reduce eNOS expression[248,249] and increase levels of caveolin-1[250]. Statins also exert direct antioxidant effects on LDL to reduce electronegative form of LDL[251,252]. Statins increase NO bioavailability by activating eNOS *via* the PI3K/Akt signaling pathway[253], agonist-stimulated eNOS-hsp90 interaction[250], and BH4-mediated eNOS coupling. This latter was demonstrated in patients with atherosclerosis[254] and in rat model of insulin resistance of diabetes[231]. These studies showed that atorvastatin increased vascular BH4 content and NO bioavailability and reduced O_2^- production *via* upregulating GTP-cyclohydrolase Ⅰ gene expression and activity. These effects occurred rapidly in patients with atherosclerosis and could be reversed by mevalonate, indicating a direct effect of vascular HMG-CoA reductase inhibition[254]. In addition, statins upregulate eNOS expression through enhancing eNOS mRNA stability. Indeed, statins increase eNOS mRNA polyadenylation through Rho-mediated changes in the actin cytoskeleton[255,256]. However, a study showed that statins can increase eNOS gene transcription by upregulating Kruppel-like factor 2 through inhibition of Rho pathway[257]. The effect of statins on eNOS expression may account for the long-term effect of stains on endothelial function. Statins also exerts antiinflammatory effects[258]. For example, atorvastatin treatment reduces proinflammatory cytokines (TNF-α, IL-1 and IL-6), intercellular adhesion molecules and C-reactive protein blood levels in hypercholesterolemic patients[259], while rapid withdrawal of statin treatment increases proinflammatory and prothrombotic biomarkers[260]. Statins were also shown vascular benefice in other inflammatory diseases such as rheumatoid arthritis[261]. Otherwise, statins increase circulating endothelial progenitor cells, likely through the PI3K/Akt pathway[262], which could contribute to long-term effects of statins on endothelial function.

Another type of LDL-lowering drugs, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, may be expected to improve endothelial function. In humans, PCSK9 mutation is closely correlated with LDL cholesterol levels and inhibition of PSCK9 with a monoclonal antibody reduces LDL cholesterol levels[263] and enhances the LDL cholesterol-lowering effect of atorvastatin[264]. Studies in cells and animals have shown that PCSK9 is associated with inflammation and endothelial cell apoptosis. In mice, systolic inflammation and OxLDL upregulate PCSK9, whereas PCSK9 interacts with macrophage, leading to NF-κB activation[265,266]. Knockdown of PCSK9 with PCSK9 siRNA or induction of gain of function mutant D374Y-PCSK9 reduces expression of stress-response genes and specific inflammation pathways, inflammation pathway activation and OxLDL-induced endothelial apoptosis[266-268]. Nonetheless, the effects of PCSK9 inhibition on human endothelial function are not yet explored.

Angiotensin-(1-7)

Angiotensin-(1-7) is a metabolite of angiotensin I under the action of various enzymes, including neutral endopeptidase, prolylendopeptidase, aminopeptidase A and neprilysin[36]. It can also be generated from angiotensin Ⅱ by prolylcarboxypeptidase[269] and carboxypeptidase (ACE2)[270]. In endothelial cells, angiotensin-(1-7) activates eNOS *via* the Mas/PI3K/Akt pathway and inhibits angiotensin Ⅱ-induced NAD(P)H oxidase activation[271,272]. Chronic treatment with angiotensin-(1-7) improves renal endothelial dysfunction associated with apolipoprotein E-deficiency[273] and diet-induced obesity in mice[274], which is likely mediated by increasing NO release[275] and eNOS expression[276,277]. Otherwise, angiotensin-(1-7) restores vascular ACE2-angiotensin-(1-7)-Mas receptor axis function that impairs ROS production by angiotensin AT1 receptor-activated NAD(P)H oxidases in hypertensive or diabetic rats[278,279]. Angiotensin-(1-7) restores NO/cGMP production and migration, decreases NADPH oxidase activity, and enhances survival and proliferation of endothelial progenitor cells isolated from the blood of diabetic patients in a Mas/PI3K/Akt-dependent manner[280]. Interestingly, overexpression of angiotensin-(1-7) gene restores the vasoreparative function of endothelial progenitor cells in mice[280]. Despite these encouraging results in cells and in animals, the information regarding the effects of angiotensin-(1-7) on human endothelial function

remains lacking.

Bradykinin

As discussed above, endogenous bradykinin exerts multiple actions that affect endothelial function. It is worth noting that bradykinin as an investigational drug protects against ROS- and toxin-induced microvascular endothelial cell death[281], and chronic treatment with bradykinin not only preserves eNOS expression in dogs with pacing-induced heart failure[101], but also upregulates eNOS and nNOS expression in vessels and in the heart of dogs with dystrophin-deficiency cardiomyopathy[19,282]. However, due to the very short half-life and implication of bradykinin in the inflammation[283] and cancers[284,285], the clinical use of bradykinin remains a challenge.

eNOS transcription enhancer

Interestingly, specific targeting eNOS transcription with a chemical compound, AVE3085, increases eNOS expression but reduces oxidative stress and platelet activation, which is associated with improved endothelium-dependent relaxation and cardiac function in animals with different experimental diseases[286-289]. This compound also prevents the inhibitory effect of ADMA on endothelium-dependent vasodilation in human internal thoracic artery rings and in pig coronary artery rings[290,291]. Thus, this compound showed a potential for the treatment of endothelial dysfunction although its effects in human clinical situations remain to be demonstrated.

I_f inhibitor, ivabradine

I_f current is an inward current carried by Na^+ and K^+, activated by hyperpolarization and conducted by hyperpolarization-activated cyclic nucleotide-gated channels (f-channels)[292]. I_f current participates in the spontaneous depolarization during Phase 4 of the action potential and plays a crucial role in the pacemaker activity of pacemaker cells located in the sinus node and atrioventricular node. Inhibition of this current by ivabradine slows down heart rate and exerts cardioprotective effects[293-296], which may involves pleiotropic actions of ivabradine[297]. Among them, beneficial effects of ivabradine on the endothelium-dependent vasodilation and on the expression of eNOS expression in both animals and humans have been reported[298-300]. Nevertheless, the effects of ivabradine on human endothelial dysfunction are controversial. Several studies did not observe significant improvement in flow-mediated vasodilation by ivabradine in patients with microvascular angina pectoris[301] or stable coronary heart disease[302] and in patients with type Ⅱ diabetes[303]. In addition, in patients with stable of coronary disease without heart failure, the additional ivabradine plus standard treatment did not improve outcome but was associated with increased frequency of atrial fibrillation, questioning the utility of this drug in the treatment of stable coronary disease[304].

Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P), a signaling sphingolipid formed by sphingosine kinase in the blood and in tissues, regulates different biological responses such as angiogenesis, vascular permeability and trafficking of T- and B-cells. S1P enhances endothelial barrier function[305,306], stimulates endothelial NO release through Akt-mediated phosphorylation of eNOS[307], and reconstitutes high density lipoproteins[308]. S1P also has antiinflammatory properties and exerts protective effect against endotoxin-induced lung injury[309,310]. Moreover, S1P exhibits a potent effect on the differentiation of adipose-derived stem cells into endothelial-like cells and upregulation of eNOS in these cells[311]. All of these properties of S1P may contribute to its endothelial protective effects. Interestingly, an orally active of S1P analogue, FTY720 also shows similar effects[312]. Thus, S1P and analogues may be used to improve endothelial function, especially in atherosclerosis and acute lung injury where presents an impairment of endothelial barrier function[313].

CONCLUSION

Endothelial dysfunction is a common mechanism involved in many cardiovascular diseases, although in some diseases such as atherosclerosis, endothelial dysfunction plays a critical role in the development of diseases, whereas in others such as essential hypertension and type Ⅱ diabetes, endothelial dysfunction generally occurs as a complication but thereafter contributes to the development and progression of organ damages. Clearly, multiple mechanisms such as inflammation, increased ROS and RNS, cellular apoptosis, increased vasoconstrictor production, decreased vasodilator production and vascular remodeling are involved in endothelial dysfunction and a specific pathology may involve more or less them as described above. However, a decreased NO bioavailability appears to play a central role because in many pathologies such as atherosclerosis, diabetes, essential and pulmonary hypertension and heart failure except for septic shock where there is a overproduction of NO, a reduction in NO bioavailability occurs sooner or later in response to different risk factors. This may explain the beneficial effects of some drugs in the treatment of a variety of cardiovascular disorders. It appears that a drug with endothelium-protective property may yield more therapeutic benefits than that without such feature. For this reason, the evaluation of endothelium-improving action may be helpful for the development of a novel cardiovascular drug. Moreover, due to the differences in risk factors contributing to the different cardiovascular diseases and the differences in mechanisms of action, treatment of endothelial dysfunction with drugs needs to be carried out according to specific mechanisms

underlying endothelial dysfunction of the disease.

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