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Endothelial dysfunction: a strategic target in the treatment of hypertension?

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Abstract Endothelial dysfunction is a common feature of hypertension, and it results from the imbalanced release of endothelium-derived relaxing factors (EDRFs; in particular, nitric oxide) and endothelium-derived contracting factors (EDCFs; angiotensin II, endothelins, uridine adenosine tetraphosphate, and cyclooxygenase-derived EDCFs). Thus, drugs that increase EDRFs (using direct nitric oxide releasing compounds, tetrahydrobiopterin, or L-arginine supplementation) or decrease EDCF release or actions (using cyclooxygenase inhibitor or thromboxane A2/prostanoid receptor antagonists) would prevent the dysfunction. Many conventional antihypertensive drugs, including angiotensin-converting enzyme inhibitors, calcium channel blockers, and third-generation β-blockers, possess the ability to reverse endothelial dysfunction. Their use is attractive, as they can address arterial blood pressure and vascular tone simultaneously. The severity of endothelial dysfunction correlates with the development of coronary artery disease and predicts future cardiovascular events. Thus, endothelial dysfunction needs to be considered as a strategic target in the treatment of hypertension.

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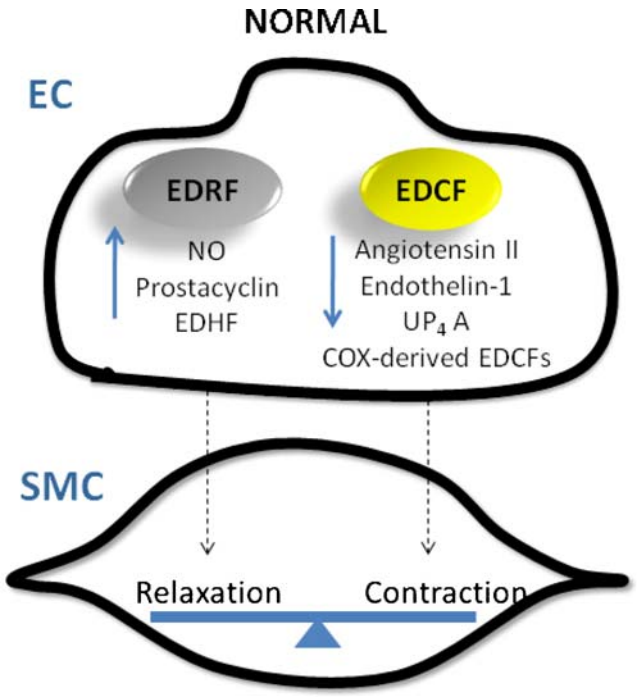
Introduction

The endothelium, the thin layer of cells that lines the interior surface of blood vessels, can be activated by various chemical and physical stimuli to simultaneously release endothelium-derived relaxing (EDRFs) and contracting (EDCFs) factors. EDRFs and EDCFs act as acute functional antagonists and exert opposing effects on the underlying vascular smooth muscles to control their tone (Fig. 1). When endothelial cells are exposed to a chronic elevation in arterial blood pressure, they age prematurely, their turnover is accelerated, and they are replaced by regenerated endothelial cells [1, 2]. However, the regenerated endothelium has an impaired ability to release EDRFs (endothelial dysfunction)—in particular, nitric oxide (NO) [3, 4]—which results in the weakening of the inhibitory brake to oppose the action of EDCFs, with ensuing prominence of endothelium-dependent contractions (constrictions) [5]. Endothelial dysfunction can trigger a chain of undesired responses, including increases in platelet aggregation, expression of adhesion molecules, and vascular smooth muscle growth [1, 6]. Thus, a vicious cycle is established, ultimately contributing to thrombosis, inflammation, vascular remodeling, and atherosclerosis.

Endothelial dysfunction has been demonstrated both in resistance arteries and conduit arteries of several hypertensive animals, including the spontaneously hypertensive rat (SHR) [7–9], the two-kidney one-clip model [10, 11], deoxycorticosterone acetate salt-treated animals [12], and the Dahl salt-sensitive rat [13, 14]. Evidence of endothelial dysfunction in human hypertension has been characterized



Q2 **Fig. 1** In healthy arteries, a normal vascular tone is maintained by the balanced release of EDRF and EDCF. This balance is tipped in hypertensive arteries with an increase in the release of EDCF and a decrease in the release of EDRF, favoring contractions. *EC* endothelial cell, *SMC* smooth muscle cell

by decreased forearm blood flow responses to endothelium-dependent vasodilator agonists, such as acetylcholine and bradykinin [15, 16], or by an increase in vasoconstrictor response to locally administered nitric oxide synthase inhibitors [17].

Endothelium-derived relaxing factors

The endothelium produces a range of EDRFs, the most significant and well-characterized of which is NO. But prostacyclin and endothelium-derived hyperpolarizing factors are also important endothelium-derived vasodilator signals, with the latter prominently contributing to endothelium-dependent relaxations in resistance arteries [18]. The majority of studies on endothelial dysfunction have concentrated on the mechanisms underlying the decreased bioavailability of NO. This decrease may result from a decrease in NO production, from a decrease in activation of guanylyl cyclase, and/or an increase in NO degradation (Fig. 2). A decrease in NO production may result from a deficiency in substrates and cofactors for NO sythases (NOS), such as L-arginine or tetrahydrobiopterin (BH_4) [13, 19]; from a decreased expression and presence of endothelial NOS (eNOS) [20]; from a decreased activation of NOS, such as phosphorylation of the enzyme or interactions with proteins (e.g., heat shock protein 90 or calmodulin) [20]; or from an increased presence of endogenous inhibitors of NOS, asymmetric dimethyl arginine in particular [21] (Fig. 2). An increase in NO degradation can result from the binding of NO to molecules such as hemoglobin and albumin, or from increased inactivation of NO by its interaction with superoxide anions [22]—a reaction which leads to the production of peroxynitrite, a toxic vascular oxidant that further contributes to vasoconstriction and vascular injury (Fig. 2). Animal and clinical studies indicate that hypertension is associated with an increase in the production of reactive oxygen species (ROS), together with a decreased level of endogenous antioxidants [23–25]. The ability of vitamin C to restore NO production and improve endothelial function in essential hypertensive patients suggests a role of oxidative stress in endothelial dysfunction in humans [25].

Endothelium-derived contracting factors

The endothelial cells can produce several EDCFs, including angiontensin II, endothelin-1, dinucleotide uridine adenosine tetrahosphate (UP_4A), cyclooxygenase (COX)-derived prostanoids, and ROS [5, 26]. When these endothelium-derived vasoconstrictors are overproduced, such as in hypertension or diabetes, they oppose the vasodilator effects of the EDRFs, exacerbating endothelial dysfunction.

Angiotensin II

Angiotensin I is metabolized into angiotensin II by endothelial angiotensin-converting enzyme (ACE). Angiotensin II can activate angiotensin receptors and trigger an increase in cytosolic calcium to mediate contractions [27]. In addition to causing vasoconstriction, angiotensin II can enhance the production of ROS—predominately through the activation of membrane-bound nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate oxidases—and thus, impairs NO bioavailability [28]. Furthermore, angiotensin II can directly stimulate the production and release of endothelin-1 and thus aggravate endothelial dysfunction [29].

Endothelin-1

There are three isoforms of endothelin (identified as ET-1, ET-2, and ET-3) that activate two subtypes of receptors (ET_A and ET_B) [30]. ET_A and ET_B receptors are found in the vascular smooth muscle and are coupled to a G_q-protein that leads to IP_3 formation [30]. IP_3 stimulates calcium release

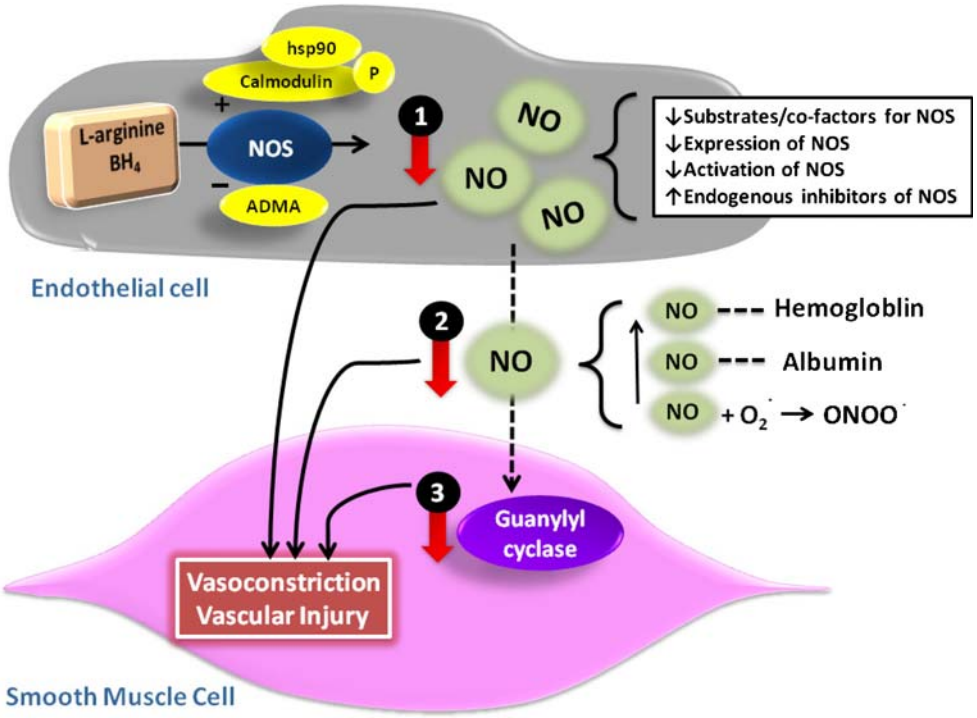


Fig. 2 Decreased bioavailability of nitric oxide may result from a decrease in NO production, an increase in NO degradation, or a decrease in the activation of guanylyl cyclase. Decreased NO production may result from deficiency in substrates and cofactors for nitric oxide synthase (NOS), decreased expression of NOS, decreased activation of NOS, or an increase in endogenous inhibitors of NOS. An increase in NO degradation can result from the binding of NO to molecules such as superoxide anions, hemoglobin, and albumin. *ADMA* asymmetric dimethyl arginine, *BH_4* tetrahydrobiopterin, *EC* endothelial cell, *hsp90* heat shock protein 90, *NOS* nitric oxide synthase, *O_2*, *ONOO* peroxynitrite, *P* phosphorylation, *SMC* smooth muscle cell

from the sarcoplasmic reticulum, which contributes to the contraction of the vascular smooth muscle [30]. Because of its powerful vasoconstrictor properties, and the retention of sodium that it causes, endothelin-1 (the main isoform produced by endothelial cells) increases arterial blood pressure. ET_B receptors are primarily located on endothelial cells, and when stimulated, they increase the release of NO and augment natriuresis and diuresis, thus lowering blood pressure [31]. The distribution of endothelin receptors on endothelial and smooth muscle cells helps to explain the phenomenon that systemic administration of endothelin-1 causes an initial transient vasodilatation (endothelial ET_B activation) and hypotension, followed by prolonged vasoconstriction and hypertension (ET_A and ET_B activation of vascular smooth muscle). Endothelin-1 can also induce the secondary release of cyclooxygenase-dependent EDCFs (presumably endoperoxides and thromboxane A_2) that cause the activation of thromboxane A2/prostanoid (TP) receptors of vascular smooth muscle [32–34].

Uridine adenosine tetraphosphate

UP_4A is a non-peptidic dinucleotide endothelium-derived vasoconstrictor that is assumed to play a role in the regulation of vascular tone [35]. UP_4A possesses both purine and pyrimidine moieties, and the contraction that it causes is mediated predominately through P2X1, and probably also through P2Y2 and P2Y4 purinoceptors. UP_4A is released from the endothelium in response to acetylcholine, endothelin-1, the calcium ionophore A23187, adenosine, and uridine triphosphate [35]. The role of UP_4A in the pathogenesis of hypertension is yet to be determined.

COX-derived EDCFs

The importance of COX-derived vasoconstrictor prostanoids has gained significant recognition in the past decade. The production of endothelium-derived prostanoids is augmented in arteries with regenerated endothelium [36, 37], and in normotensive aging and hypertensive arteries [5, 7, 9, 38]. The endothelium of the renal arteries of healthy rats also releases EDCF, suggesting that it may play a role in the regulation of basal tone in this artery, and not only during agonist-induced stimulated release [39, 40]. Studies in humans show that the acetylcholine-induced vasodilatation is diminished in conductance and resistance vessels of patients with hypertension. In these hypertensive patients, intra-arterial administration of the COX inhibitor indomethacin improved the vasodilator response to acetylcholine [41, 42], suggesting that the production of COX-derived EDCF contributes to the onset of endothelial dysfunction in human hypertension.

Mechanisms underlying the production of COX-derived EDCFs

In brief, the chain of events leading to endothelium-dependent contractions requires an abnormal increase in

intracellular calcium in the endothelial cells [5, 26]. The rise in calcium activates phospholipase A_2 to release arachidonic acid from the cell membrane phospholipids. Then COX breaks down arachidonic acid to form prostanoids that activate TP receptors located in the vascular smooth muscle, resulting in contraction [5, 26]. During the production of prostanoids, COX simultaneously produces ROS, which can subsequently stimulate COX within the smooth muscle and produce more prostanoids [5, 26], thus amplifying the TP receptor-mediated response (Fig. 3).

Calcium overload

An abnormal, high accumulation of intracellular calcium in endothelial cells is critical and triggers the production of COX-derived EDCFs [43] (Fig. 3). Stimulation with acetylcholine results in calcium overload in the aortic endothelial cells of SHR, but not in normotensive Wistar Kyoto rats (WKY), signifying dysfunction of calcium handling in the hypertensive strain [43]. When calcium overload is mimicked in WKY arteries using calcium-increasing agents (such as the calcium ionophore A23187 or cyclopiazonic acid), endothelium-dependent contractions are evoked despite the normal arterial blood pressure of the animals. Nonetheless, the amplitude of the contraction remains larger in SHR than in WKY [43]. This is explained best by the increased expression of COX and prostanoid synthases, a greater release of prostanoids, as well as a hyper-responsiveness of the TP receptors in the aortas of SHR than in that of WKY [5, 44–46]. Hence, all these downstream modifications are not a prerequisite for the development of endothelium-dependent contractions, but their presence amplifies the response.

COX activity

The activity of COX is required for the generation of vasoconstrictor prostanoids. Two isoforms of COX, a constitutive form (COX1) and an inducible form (COX2), have been cloned and characterized [47]. Yet COX1—termed as the constitutive isoform—can be over-expressed under certain conditions, such as increases in shear stress [47]. Inflammation is the most common cause for the up-regulation of COX2 [47]. Multiple studies using arteries from mice and rats have confirmed that COX1 is the primary isoform involved in endothelium-dependent contractions. For example, endothelium-dependent contractions are abolished by selective COX1 inhibitors, but are relatively insensitive to selective COX2 inhibitors [9, 48]. Furthermore, endothelium-dependent contractions occur in the aortas of wild-type and $COX2^{-/-}$ knockout mice, but not in those of $COX1^{-/-}$ knockout mice [49]. Later studies using hamster aortas [50] and aging rats [51], however, showed that COX2 can contribute equally to the contraction when present or induced in the endothelial cells.

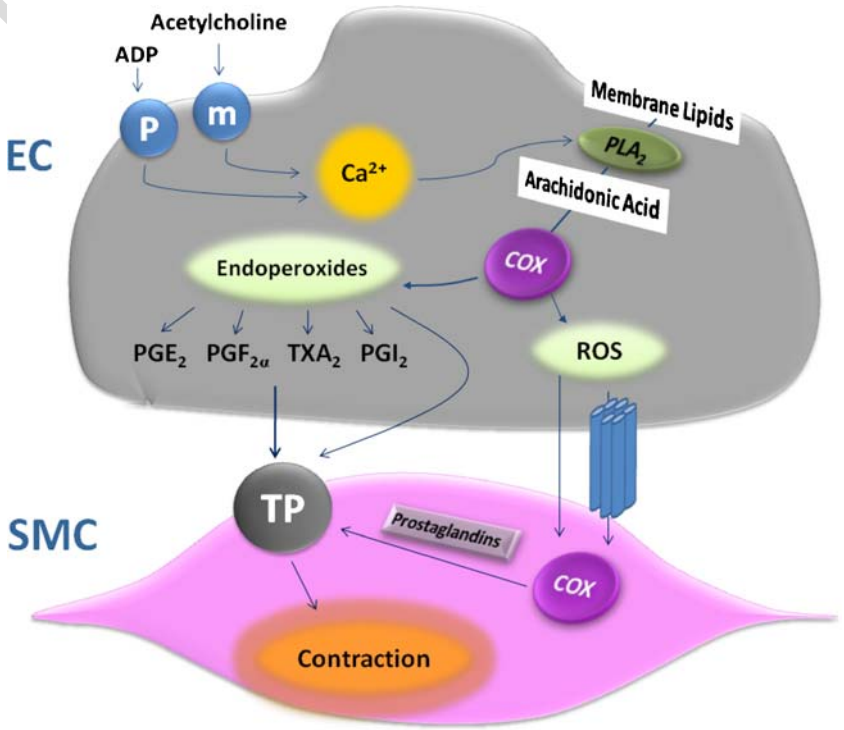


Fig. 3 Endothelium-dependent contraction has two components: the generation of prostaglandins and ROS. A rise in calcium activates phospholipase A_2 (PLA_2) to release arachidonic acid, which is subsequently metabolized by cyclooxygenase (COX) to form endoperoxides and various prostaglandins that activate TP receptors located at the vascular smooth muscle. COX also produces ROS, which diffuses or possibly transmigrates via gap junctions and stimulates COX within the smooth muscle, producing more prostanoids and amplifying TP receptor-mediated contractions. *ADP* adenosine diphosphate, *m* muscarinic receptors, *P* purinergic receptors, PGE_2 prostaglandin E_2, $PGF_{2\alpha}$ prostaglandin $F_{2\alpha}$; PGI_2 prostacyclin, *ROS* reactive oxygen species, TXA_2 thromboxane A_2

Production of prostanoids

The immediate products of COX are the endoperoxides, which themselves function as vasoconstrictors by binding to TP receptors [45]. Endoperoxides are further transformed into prostacyclin, thromboxane A_2, prostaglandin E_2, prostaglandin $F_{2\alpha}$, and prostaglandin D_2 by their respective prostanoid synthases (Fig. 3). Prostacyclin synthase is by far the most abundant prostanoid synthase expressed in the endothelium [52]. Its expression is augmented in the aorta of SHR compared with that of WKY [52, 53], suggesting that chronic hypertension induces the protein. In line with this observation, there is an exaggerated release of prostacyclin in the aorta of the hypertensive rat [46, 54, 55]. Since this classical vasodilator prostanoid does not mediate relaxation in this artery, it instead evokes contraction through activation of TP receptors at high concentrations [44]. In response to acetylcholine, prostacyclin and endoperoxides are the key mediators of endothelium-dependent contractions in the rat aorta [5, 44]. Whether or not prostacyclin plays a detrimental role as EDCF in other animal models or in humans remains to be demonstrated.

Under certain pathological conditions involving enhanced oxidative stress, ROS interacts with NO to form peroxynitrite [22], which can significantly inhibit the activity of prostacyclin synthase by tyrosine nitration of the enzyme [56, 57]. Under such circumstances, there is a marked compensatory production of prostaglandin E_2 and prostaglandin $F_{2\alpha}$, leading to greater importance of these two prostanoids [46, 56, 58]. In the hamster aorta and in human renal arteries, there is a high expression of COX2 and a prominent release of prostaglandin $F_{2\alpha}$, indicating the importance of this prostanoid as the EDCF in these arteries [50]. Likewise, prostaglandin $F_{2\alpha}$ is the major EDCF released from re-endothelized femoral rat arteries [36].

When endothelium-dependent contractions are evoked by the calcium ionophore A23187 or adenosine diphosphate (ADP) in the aorta of SHR, the response is partly sensitive to inhibitors of thromboxane synthase [54, 55, 59], implying the involvement of thromboxane A_2. The mRNA expression of thromboxane synthase is enhanced in the aorta of SHR compared to WKY [52]. Direct chemical detection with immunoassays has revealed that A23187 and ADP stimulate the release of thromboxane A_2 and endoperoxides [46, 54, 55], suggesting that these prostanoids are the key mediators of endothelium-dependent contraction during exposure to these agonists.

On the whole, there is a marked heterogeneity in the formation of EDCF. The precise chemical identity of EDCF varies depending on the stimulus, the vascular bed, the age, and the physiopathological condition of the donor animal. Thus, prostacyclin, thromboxane A_2, prostaglandin E_2, prostaglandin $F_{2\alpha}$, and ROS all have been proposed as COX-derived EDCF. It is important to keep in mind that endothelium-dependent contractions are unlikely to be due a single substance, but rather likely are evoked by a mixture of these endothelium-derived products (Fig. 3).

The involvement of TP receptors

Prostanoid receptors are classified into five discrete types based on their sensitivity to the five naturally occurring prostanoids: prostacyclin I_2, thromboxane A_2, prostaglandin D_2, prostaglandin E_2, and prostaglandin $F_{2\alpha}$. They are termed P receptors—IP, TP, DP, EP, and FP—with the preceding letter indicating the prostanoid to which they are the most sensitive. The effectiveness of TP receptor inhibitors in abolishing endothelium-dependent contractions pinpoints the involvement of this prostanoid receptor subtype in the response [48, 60–62]. Although thromboxane A_2 is the most potent agonist towards TP receptors, it is not its exclusive ligand. All other prostanoids can bind to TP receptors and mediate contraction, but with varying potency. The mRNA and protein expression of TP receptors does not differ in the aortas of WKY and SHR, indicating that their expression level is not altered by the hypertensive process [52, 63]. However, the vascular smooth muscle of the SHR aorta exhibits a greater responsiveness than that of the WKY to the constrictor effect of endoperoxides acting at TP receptors [45]. An involvement of other prostanoid receptors in endothelium-dependent contractions has been suggested [63–65], but non-TP receptor endothelium-dependent component appears to constitute a small part of the full response.

A separate ROS component

During the production of prostanoids by endothelial COX, ROS are formed simultaneously. These COX-derived ROS can act as vasoconstrictors [43, 62]. Thus, COX-derived EDCF-mediated contractions can be attributed to two components—prostanoids or ROS [5] (Fig. 3). The possible existence of a separate ROS component in endothelium-dependent contractions is strengthened by the following observations: First, that the generation of ROS by xanthine plus xanthine oxidase in the extracellular bathing fluid evokes a contraction in the aorta without endothelium that requires the activity of COX and stimulation of TP receptors [62, 66], suggesting that endothelium-derived ROS could stimulate COX in the vascular smooth muscle with resulting prostanoid production, causing more TP receptor-mediated contraction. Second, the direct application of hydrogen peroxide, but not that of superoxide anions or hydroxyl radicals, triggers contractions in the rat

aorta that are sensitive to cyclooxygenase inhibitors and TP receptor antagonists [66–69], suggesting that hydrogen peroxide is the mediator responsible for the ROS component of endothelium-dependent contraction. Myoendothelial gap junctions may facilitate the transfer of ROS from endothelial cells to smooth muscle cells [70]. In the aorta of the SHR, both the prostanoid and ROS component appear to contribute equally to the final endothelium-dependent contractions, as antioxidants only partly reduce the response [62]. By contrast, in the canine basilar artery, endothelium-dependent contractions are fully prevented by superoxide dismutase plus catalase [71], indicating that the response is dominated by the endothelial ROS component.

Therapeutic interventions to improve endothelial function in hypertension

Considering the marked endothelial dysfunction in hypertension and since its severity correlates with the development of coronary artery disease and predicts future cardiovascular events [72], this dysfunction has to be considered as a central target in the treatment of hypertension. Theoretically, drugs targeted to increase the release of EDRF (and in particular, NO), and drugs that decrease the production or action of EDCF, should reduce endothelial dysfunction.

Improving NO production

Direct NO releasing compounds, such as nitroglycerin, are effective vasodilators. However, continuous administration comprises a clinical problem due to the desensitization of the target enzyme guanylyl cyclase, leading to cross-tolerance to other endothelium-dependent vasodilators [73]. Other concerns involve the ability of nitroglycerin to increase ROS indirectly [74].

Acute supplementation with BH_4, an essential cofactor of NOS, improves endothelial dysfunction by increasing NO and reducing ROS in many experimental animal studies [75]. But a clinical trial of the effects of BH_4 on arterial blood pressure in subjects with poorly controlled systemic hypertension has been terminated for lack of significant beneficial effect [76]. By contrast, positive results have been reported with the use of BH_4 to treat endothelial dysfunction in patients with sickle-cell disease [76]. The dissimilar results in these clinical trials highlight the importance of fully addressing basic questions about the mechanism of endothelial regulation that will be critical in the design of BH_4-based therapies.

Endogenous NO formation is largely dependent on the extracellular concentrations of its substrate, L-arginine. Supplementation of L-arginine leads to a measurable decline in blood pressure and improved endothelial functions in experimental animals and in hypertensive patients [77, 78]. Most L-arginine studies to date have used high daily doses, due to the pharmacokinetics of oral L-arginine, which reaches its highest concentration in the blood within an hour and then diminishes quickly [77]. The use of sustained-release L-arginine products in hypertensive patients shows promising signs of improving endothelial function [79].

When arteries are exposed to NO, whether released from the endothelial cells or added exogenously, this causes a long-term inhibition of endothelium-dependent contractions [80–83]. This implies a suppressed occurrence of EDCF-mediated contractions under conditions where there is an adequate release of NO. Thus, NO-enhancing agents not only will enhance vasodilatation, but also will hamper the occurrence of endothelium-dependent contractions.

Reducing arterial blood pressure

Antihypertensive treatments—such as ACE inhibitors, calcium channel blockers, and third generation β-blockers—reverse endothelial dysfunction in experimental animals and in hypertensive patients [84, 85]. Several effects of ACE inhibitors enhance NO release and bioactivity, including preventing the breakdown of endogenous bradykinin (a potent NO releaser) [85]. ACE inhibitors also protect NO bioavailability [85]. The beneficial effect of calcium channel blockers on endothelial dysfunction can be attributed to their ability to reduce calcium entry through voltage-dependent channels of the vascular muscle cells, thereby dilating large conduit and resistance arteries [86]. In addition, drugs such as amlodipine activate eNOS to release more NO [87, 88]. Other calcium channel blockers, such as lacidipine, possess antioxidant properties [89], while third-generation β-blockers such as carvedilol and nebivolol, in addition to their adrenergic blocking characteristics, substantially improve endothelial dysfunction through their strong stimulatory effect on the activity of endothelial NOS and their antioxidative properties [90]. Blood pressure reduction per se does not guarantee improvement in endothelial dysfunction. Other antihypertensive drugs, such as conventional β-adrenergic blockers, reduce arterial blood pressure but fail to restore normal endothelial function [85].

Preventing EDCF-mediated responses

Because prostacyclin is one of the main mediators of endothelium-dependent contractions in the response of acetylcholine, inhibition of its production may result in the improvement of endothelial function. But prostacyclin also is beneficial to the vascular system because of

its ability to prevent aggregation of platelets and avoid thrombosis [91]. In addition, inhibition of prostacyclin synthase results in the build-up of endoperoxides (which by themselves activate TP receptors) and the shunting of the latter to other synthases, which produce more potent vasoconstrictor prostanoids [46, 54, 55]. Therefore, selective inhibition of prostacyclin synthase would not reduce the occurrence of unwanted endothelium-dependent contractions, but rather would result in amplified worsening of the vascular complications. In the SHR aorta, thromboxane A_2, and endoperoxides are the main EDCF in response to A23187 and adenosine diphosphate [44, 54, 55]. In the aorta of the hamster, in response to acetylcholine, the main EDCF is prostaglandin $F_{2\alpha}$ [50]. Thus, the contribution of various prostaglandins released during endothelium-dependent contractions varies depending on the stimulus, the artery, the species, and the disease state of the donor. It therefore appears more desirable to design drugs that target either upstream or downstream of the EDCF cascade, rather than individual prostanoid synthases, to alleviate EDCF-mediated endothelial dysfunction.

Depending on the availability of the enzyme, both COX1 and COX2 can contribute to endothelium-dependent contractions. Thus, the use of selective drugs targeting a specific isoform of COX is not the rationale of choice to inhibit endothelium-dependent contractions in hypertension. Moreover, the use of non-selective COX inhibitors are linked with multiple adverse effects, including peptic ulceration and dyspepsia, while selective COX-2 inhibition increases the risk of myocardial infarction, thrombosis, and stroke [92].

EDCFs ultimately converge to activate TP receptors [48, 60–62]. Although other prostanoid receptors may contribute [63–65], it seems—at least from data obtained in animal studies—that TP receptors are the dominant receptor subtype involved. The TP receptor blocker terutroban improves endothelial function in patients with coronary disease [93], which illustrates the role of vasoconstrictor prostanoids in human endothelial dysfunction. Thus, selective TP receptor antagonists may be the most logical therapeutic tools to intervene with endothelium-dependent contractions in hypertension. Epoxyeicosatrienoic and dihydroxyeicosatrienoic acids function as endogenous TP-receptor antagonists and induce vasodilatation [94], suggesting their use as novel TP receptor inhibitors. Synthetic TP receptor blockers (such as terutroban) effectively prevent endothelium-dependent contraction in numerous hypertensive experimental animal models [7, 48, 51, 60–62]. The prospective use of TP-receptor antagonists in correcting the consequences of the imbalanced release of endothelium-derived vasoactive substances in hypertensive patients deserves further exploration.

Conclusion

The endothelium is one of the major target organs that are damaged by high blood pressure. Chronic elevation in blood pressure accelerates the turnover of endothelial cells, causing them to age prematurely. The regenerated endothelium has an impaired ability to release EDRF and favors the occurrence of endothelium-dependent contractions. Endothelial dysfunction triggers a chain of undesired responses, including increased platelet aggregation, expression of adhesion molecules, and vascular muscle growth—ultimately leading to thrombosis, inflammation, vascular remodeling, and atherosclerosis. Endothelial dysfunction therefore should be considered as a central target in the treatment of hypertension. Mechanisms that increase EDRF or decrease the release/bioavailability action of EDCF are promising drug targets to mitigate the damage caused by endothelial dysfunction.

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