COMMENTARY

A weapon of endothelial cells for fighting vascular disease

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Vascular endothelial cells, of which there are roughly 10^{14} in the human body, produce various factors that have important roles in the regulation of vascular tone. An amazing weapon of endothelial cells for fighting vascular disease is endothelial nitric oxide synthase (eNOS), which is an enzyme that generates a key vasoprotective factor, nitric oxide (NO). NO regulates vascular tone by inhibition of platelet aggregation and adhesion, suppression of vascular smooth muscle cell proliferation, prevention of oxidative modification and decrease of proinflammatory gene expression.¹ All of these factors contribute to the progression of atherosclerosis. Indeed, impaired endothelial function has been found in the arteries of the forearm, coronary arteries and renal vasculature in hypertension, diabetes mellitus, dyslipidemia and coronary artery disease.² Endothelial dysfunction is an early feature of atherosclerosis and vascular disease in humans.³ One possible mechanism of endothelial dysfunction is a decrease in NO bioavailability. Endothelial function has been shown to be associated with an imbalance between NO and ROS, so-called oxidative stress.

In this issue of *Hypertension Research*, Satoh *et al.*⁴ focus on endothelial dysfunction and oxidative stress in Dahl salt-sensitive hypertensive rats. The authors have recently developed a novel method to directly detect NO and ROS at the same time using fluorescent probes. In this paper, the authors show that in the kidney, NO but not ROS was detected in the glomeruli and arterioles of

normotensive rats; however, ROS production was increased and NO production was decreased in Dahl salt-sensitive hypertensive rats. The authors also previously reported the same pattern, an imbalance of ROS/NO, indicating increased oxidative stress in the kidneys of diabetic and metabolic syndrome model rats.^{5,6} What is the cause of the increased oxidative stress? The authors have clearly shown that NAD(P)H oxidase and uncoupled eNOS are major sources of increased oxidative stress in Dahl salt-sensitive hypertensive rat kidneys. An especially noteworthy result is that eNOS uncoupling exists in the glomeruli of Dahl salt-sensitive hypertensive rats. Previously, the authors had reported the existence of uncoupled eNOS in a diabetic model rat kidney.^{5,7} eNOS produces ROS rather than NO under conditions of eNOS uncoupling through a deficiency of tetrahydrobiopterin (BH_4), an essential cofactor for eNOS (Figure 1). In turn, a deficiency of BH_4 caused by ROS leads to down-regulation of eNOS.⁸ Supplementation with BH_4 improved endothelial function in both

in vitro and *in vivo* experiments. Moreover, this supplementation effect has already been proven in smokers and patients with hypertension, hypercholesterolemia or chronic heart failure.^{9–11} In this study, the authors examined the expression of GTPCH1, which is the rate-limiting enzyme in BH_4 synthesis, and the findings are consistent with those in previous reports. Recently, Higashi *et al.*¹² also showed that the grade of oxidative stress correlates with BH_4 deficiency and that supplementation with BH_4 augmented endothelium-dependent vasodilation in the brachial arteries of elderly patients. Satoh *et al.*⁴ showed this indirectly by showing decreased plasma levels of BH_4 and increased plasma levels of BH_2 . On the basis of previous findings combined with the data from the current study, it is suggested that BH_4 deficiency and decreased eNOS activity cause endothelial dysfunction through an increase in oxidative stress in atherosclerotic patients with hypertension, diabetes and metabolic syndrome. It is true that there are several pathways to increase oxidative stress other than eNOS

Figure 1 eNOS uncoupling can progress the pathogenesis of endothelial dysfunction.

uncoupling; however, in terms of NO bio-availability, eNOS has the most important role to fight vascular disease.

Moreover, the authors have shown an interesting finding that the renal autoregulatory mechanism was impaired in the early stages of hypertension onset. According to the results of this study, the capacity to autoregulate the steady-state renal flow in response to step changes was decreased in Dahl salt-sensitive rats fed a high-salt diet compared with those fed a low-salt diet. Then, the authors focused on the P2rx1 gene, which encodes a protein belonging to the family of purinoceptors for ATP. This receptor functions as a ligand-gated ion channel with relatively high calcium permeability. Binding to ATP mediates synaptic transmission between neurons and from neurons to smooth muscle; this binding is responsible, for example, for renal microcirculation and for sympathetic vasoconstriction in small arteries, arterioles and vas deferens.¹³ The authors observed decreased mRNA expression of P2rx1 in hypertensive rat glomeruli by real-time PCR. Thus, the authors speculate that P2rx1 expression was decreased as a result of renal damage caused by hypertension and that this decrease may have led to the impairment of renal autoregulation.

In cultured endothelial cells, the application of antioxidants increases eNOS activity via regeneration of BH₄.¹⁴ Long-term *in vivo* vitamin C treatment restored endothelial function and eNOS activity in the aorta of Apoe^{-/-} mice. In patients with coronary heart disease, acute infusion of high-dose vitamin C has been found to improve endothelial function. Thus, vitamin C may improve endothelial function; however, a clear mechanism is not yet known.¹⁵ In addition, there is no evidence showing that vitamin C supplementation reduces the risk

of cardiovascular morbidity or mortality.¹⁶ Thus, the efficacy of vitamin C in preventing endothelial dysfunction seems to be controversial. Of the existing drug classes used to treat vascular diseases, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs) and statins, have been shown to reduce vascular oxidative stress, improve endothelial dysfunction and ultimately provide a prognostic benefit. Importantly, the authors showed that treatment with an ARB, telmisartan, restored the ROS/NO balance in the kidney and probably in the vasculature, leading to improvement in endothelial dysfunction in the aorta. Moreover, telmisartan has been shown to restore the renal P2rx1 expression to control levels, leading to improvement in renal flow autoregulation. It is well known that ARBs decrease ROS production and that this decrease may have a renoprotective effect. Through suppression of ROS, the authors have elucidated the role of P2rx1 in hypertensive renal damage. ARB may regulate renal P2rx1 expression and autoregulation in hypertension. The results of this study may strengthen the case for ARB use for renoprotection in hypertensive patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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