Beyond Blood Pressure

Endothelial Protection Against Hypercholesterolemia by Angiotensin II Type-1 Receptor Blockade

Henning Morawietz

Hypercholesterolemia and an activated renin-angiotensin-aldosterone system are well-established independent cardiovascular risk factors. Several lines of evidence support an important role of modified LDLs and angiotensin II in the development and progression of atherosclerosis. Angiotensin II is not only a potent vasoconstrictor, but it also promotes proinflammatory and prothrombotic properties of vascular cells. A growing body of in vitro studies shows the induction of cellular adhesion molecules and cytokines by angiotensin II in endothelial cells. In vivo, angiotensin II promotes leukocyte–endothelial cell interaction in the microcirculation. This proinflammatory mechanism involves the redox-sensitive mobilization of adhesion molecules such as P-selectin. These and several additional findings in cell systems and large vessels support a crucial role of the angiotensin II type-1 (AT₁) receptor–mediated formation of reactive oxygen species (ROS) in the pathogenesis of atherosclerosis. However, the impact of AT₁ receptor antagonism on the accelerated inflammatory and thrombotic response and ROS formation by hypercholesterolemia has not been studied in the microcirculation in vivo so far.

In this issue of Hypertension, Petnehazy et al provide experimental evidence for the endothelial protection by AT₁ receptor antagonism against inflammatory and thrombogenic responses to hypercholesterolemia. The authors describe in this very interesting study a decreased platelet and leukocyte adhesion after losartan treatment in postcapillary venules of mice with hypercholesterolemia. This endothelial protection is not mediated by direct effects on blood pressure or serum cholesterol. The systemic AT₁ receptor antagonist prevents the augmented oxidative stress in hypercholesterolemic microcirculation. Hypercholesterolemia increases AT₁ receptor expression itself, which is prevented by losartan treatment. Using platelet infusion protocols, the authors provide strong evidence that this protective effect of AT₁ receptor blockade is primarily mediated by the endothelium but not by the platelets. These data support a crucial role of the endothelial AT₁ receptor in the thrombogenic and inflammatory responses to hypercholesterolemia.

The putative role of cellular adhesion molecules in this protective action of AT₁ receptor blockade is not fully resolved yet. It was shown recently that angiotensin II can modulate the expression of adhesion molecules in vivo. Although P-selectin is upregulated by hypercholesterolemia in several vascular beds, the antiadhesive effect of AT₁ receptor antagonism seems to involve additional adhesion molecules.

Another mediator of the vasoprotective effects of AT₁ receptor blockade in hypercholesterolemia could be increased oxidative stress. Oxidized LDL and angiotensin II have been shown to induce the NAD(P)H oxidase and superoxide anion formation in endothelial cells. Angiotensin II can increase the uptake of oxidized LDL by the lectin-like oxLDL receptor-1 (LOX-1) in the vessel wall. This could result in a proatherosclerotic vicious cycle of increased NADPH oxidase–dependent superoxide anion formation, augmented generation and uptake of oxidatively modified LDL, and further potentiation of oxidative stress by oxidized LDL and angiotensin II in endothelial cells.

The AT₁ receptor plays a key role in this process. Treatment with AT₁ receptor antagonists blocks the augmented endothelial oxidative stress and oxidized LDL uptake in response to angiotensin II in vitro. In animal studies with high-cholesterol diet, hypercholesterolemia induced the LOX-1 expression in neointima of aortas. This can be reduced by treatment with losartan. AT₁ receptor blockade improved the hypercholesterolemia-associated endothelial dysfunction. Furthermore, AT₁ receptor blocker therapy reduced NAD(P)H oxidase subunit expression in arteries from patients with coronary artery disease.

How oxidative stress affects the described anti-inflammatory and antithrombotic properties of AT₁ receptor antagonism is currently still under debate. An attractive hypothesis supports a crucial role of the vascular ROS/NO balance. Because ROS can rapidly react with NO, the well-described antiadhesive and antithrombotic properties of NO could be affected. Furthermore, growing evidence supports an important role of ROS as cellular signaling molecules modulating the expression of adhesion molecules. However, the underlying molecular mechanisms in vivo have to be worked out in more detail.

The endothelial protection against hypercholesterolemia by AT₁ receptor blockade might have interesting clinical implications. The actions of losartan on platelet adhesion suggest the possibility that treatment with AT₁ receptor blockers may reduce the risk of thrombotic events in patients with cardio-

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vascular diseases. The AT1 antagonist losartan corrected the altered structure and endothelial dysfunction of resistance arteries from patients with essential hypertension, whereas a β-blocker had no effect. Recently, the AT1 receptor blocker irbesartan reduced high-sensitive C-reactive protein, interleukin-6, and platelet aggregation in patients with coronary artery disease, suggesting even a stronger anti-inflammatory and antiaggregatory effect compared with angiotensin-converting enzyme inhibition. Several recently completed megatrials with cardiovascular end points support a vasoprotective potential of AT1 receptor blockers. AT1 receptor antagonism reduced mortality and morbidity in patients with chronic heart failure and left ventricular systolic dysfunction. Furthermore, in patients with metabolic syndrome, AT1 receptor blockers seem to have beneficial effects on the progression of endothelial dysfunction and the onset of type 2 diabetes.

Although many open questions remain, AT1 receptor blockers have a promising therapeutical potential, which seems to include anti-inflammatory and antithrombotic properties beyond blood pressure. A balanced combination of AT1 receptor blockade and cholesterol-lowering drugs might even act synergistically on vascular oxidative stress and platelet and leukocyte adhesion. However, ongoing experimental and clinical studies will bring further light into this interesting and promising field.

References
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