Investigating the mechanisms of atherosclerosis, the number one cause of death in the civilized world, is an arduous task. During the last 5 decades, many aspects of atherosclerotic lesion development have been revealed and many hypotheses have been tested. Thanks to this gigantic effort, our knowledge of vascular biology and engaged pathogenic mechanisms have grown enormously. In spite of all this work, time, and money spent in thousands of laboratories all over the world, atherosclerosis remains something of an unsolved mystery. Every problem solved and every question answered raises even more questions and debates. This is largely because of the fact that there is not one single factor driving atherogenesis but many. However, there are some factors which have remained on stage for many years and from which a considerable part of the scientific community is willing to claim that these players deserve long-term attention. Among these, angiotensin II has been recognized as a major driving force behind endothelial dysfunction and atherosclerotic plaque development. Supposedly, generation of reactive oxygen species, activation of proapoptotic pathways, vascular smooth muscle cell (VSMC) proliferation, proinflammation, enhanced endothelial degeneration, and reduced vascular regeneration resemble mechanisms underlying the proatherosclerotic properties of angiotensin II.

In the present issue of Hypertension, Weiss and Taylor investigated a low renin model of hypertension and present data which underline the key role of angiotensin II in atherogenesis. Deoxycorticosterone acetate (DOCA) salt induced hypertension is an often used model. What makes this model unique is the fact that DOCA salt induced hypertension is accompanied with a decline in serum renin levels and a reduction in systemic angiotensin II release. One would imagine that this model might be well suited to investigate proatherosclerotic factors independent on Ang II.

As shown by the Taylor group, ApoE-/- mice made hypertensive by implantation of DOCA salt tablets develop rapid atherosclerosis. Surprisingly, this effect is prevented by administration of either an angiotensin type 1 (AT1) receptor blocker or an angiotensin-converting enzyme (ACE) inhibitor. Of note, neither drug affected blood pressure, as assessed by the tail cuff method, in this DOCA salt model of hypertension and concomitant atherosclerosis. Weiss et al postulate that the described effects are not mediated via attenuation of the already weak systemic but the tissue connected renin-angiotensin-system (RAS) of the vasculature. This notion is supported by immunostainings showing elevated levels of angiotensin II, ACE, and the AT1 receptor in aortas of hypertensive ApoE-/- mice.

Recent publications underline the finding that angiotensin II and the activated AT1 receptor are key players during the development of vascular lesions. It has been shown previously that angiotensin II infusion independently results in accelerated atherosclerosis and aneurysm formation on blood pressure in the same animal model. Doran et al investigated apolipoprotein (Apo)E-/- mice receiving high cholesterol diet and treatment with either an AT1 receptor antagonist or a calcium channel blocker. Only the AT1 receptor antagonist treatment attenuated the development of atherosclerotic lesions, although both drugs reduced blood pressure levels at the same rate. Furthermore, experiments in double knockout animals devoid of AT1 receptors and either ApoE or LDL receptors revealed that the absence of AT1 receptors profoundly reduced athrogenesis despite the fact that the lipid disorder prevailed.

Two critiques which apply to all of these studies have to be mentioned. First, there is the fact that blood pressure measurements were taken via the tail cuff method which is less than ideal. Second, there are some limitations inherited in the DOCA salt model, eg, potential interactions between mineralocorticoid receptors and Ang II signaling as shown previously by several investigators.

As already mentioned, underlying mechanisms of vascular lesion development involve oxidative stress, proinflammation, increased endothelial apoptosis, and impaired function of supposedly bone marrow-derived progenitors. However, the present article is not a mere confirmation of the already known facts, but importantly extends our understanding of the interplay of the RAS and vascular tissue. The animals used are not a model in which one would consider the RAS as a major problem at all—as is true for many of our patients who are not suffering from heart failure or acute large myocardial infarction and still are afflicted by atherosclerosis. Those observations suggest that the tissue-based components may be of even greater importance than the circulating hormones. One may speculate that (1) RAS inhibition adds antiatherogenic effects to the vasoprotective mechanisms mediated by blood pressure lowering alone and that (2) the tissue resident RAS might be of much higher importance than presently anticipated.
From the mechanistical point of view, most homework remains undone—despite or because of the achieved findings. How do vascular cells, T-cells, and macrophages contribute to Ang II release? Which factors promote local angiotensin II release and AT₁ receptor activation? What are local and cellular mechanisms of Ang II–induced NADPH-oxidase activation? If local factors are of great importance, how can we combine these thoughts with novel results on the importance of circulating regenerative cells from nonvascular depots such as the bone marrow? Are we looking at atherogenesis as a consequence of AT₁ receptor activation? The fact that both AT₁ receptor antagonists and ACE inhibitors did the job in the current study point to the importance of the AT₁ receptor. However, there is evidence that besides AT₁ receptor activation, AT₂ receptor stimulation during blockade of AT₁ receptors is of significance, especially in conjunction with increasing levels of circulating angiotensin II levels. But then, if the local RAS is of such importance, do these feedback mechanisms apply to the tissue-resident situation? Do we have relevant local expression of AT₁ receptors? These are some of the questions which have to be answered via in vitro and in vivo studies in future.

It is an interesting situation that although we are still in the process of understanding mechanisms and elucidating effects of angiotensin II blockade, this class of drugs is already widely used for treating patients.

Do the findings of Weiss et al correspond to the human situation? Yes and no. The fact that simple blood pressure reduction with drugs such as hydralazine exerts atheroprotection in the DOCA-salt model indicates that blood pressure reduction is the number one goal in our patients. In addition, many mega-trials failed to reveal major differences between RAS-based and other drug regimes. This could be because of the limited follow up period and the selected patient population. Other studies provide evidence for the superiority of ACE inhibitors or AT₁ receptor antagonists. The investigators of the LIFE-study reported a significantly reduced vascular reduction with drugs such as hydralazine exerts atheroprotection? If this true, why are coronary events not similarly reduced?

The study which greatly fuelled the hypothesis of angiotensin II and atherosclerosis was the HOPE study. The ACE inhibitor Ramipril profoundly reduced numerous cardiovascular end points in a high risk group of individuals despite a very modest blood pressure reduction. We are still awaiting the ultimate proof and the answer to the question whether AT₁ receptor antagonism (and concomitant AT₂ receptor agonism), ACE inhibition, or the combination of both (strong global RAS suppression) is most effective in reducing atherosclerosis-driven events. The ONTARGET study will soon resolve some of these burning issues. It will surely deliver additional unresolved questions, which may then partly be reiterated after publication of the ALTITUDE trial in which a global RAS suppression strategy via an renin inhibitor will be tested in terms of atheroprotection. Until then, we are all invited to get engaged in further mechanistical cellular, animal, and human studies, to participate in thoughtful debates, and to gain further research energies by virtue of the evergreen angiotensin II.

Disclosures

None.

References

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Cornelius F.H. Mueller and Georg Nickenig

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