Renin inhibition and atherosclerosis*

Friedrich C. Luft

Medical Faculty of the Charité, Helios Klinikum-Berlin, Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine, Berlin, Germany

Keywords: ACE inhibitors; aliskiren; angiotensin II; bone marrow; renin

Angiotensin II (Ang II) has long been considered the major bioactive effector molecule of the renin–angiotensin system and is recognized as a major contributor to hypercholesterolaemia-induced atherosclerosis [1,2]. LDL-receptor-deficient and apoE-deficient mice have been intensively investigated in this regard. Chronic Ang II infusions in such mice accelerate atherosclerosis and promote aneurysm formation [3]. Angiotensin converting enzyme (ACE) inhibitors and angiotensin AT1 receptor blockers (ARB) reduce the atherosclerotic lesion size [3]. The results would suggest that reduced Ang II levels and decreased signalling through AT1 receptors are responsible for the salubrious effects of these drugs. However, some have argued that perhaps increased signalling via AT2 receptors in the case of ARB or perhaps the bioactive angiotensin peptides Ang III, Ang IV or Ang (1–7) play a role. The latter molecule is said to exert protective effects by signalling through the Mas receptor. ACE inhibitors could also exert their effects by augmenting N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), a haematopoietic stem cell proliferator inhibitor that is degraded by ACE. Finally, perhaps ACE inhibitors really do work by increasing bradykinin. One way around these somewhat peripheral and far-fetched explanations would be to inhibit renin directly. By doing so, Ang I production should decrease dramatically. Ang II should diminish and all these pesky breakdown products that we do not understand should be diminished (Figure 1). Furthermore, AcSDKP production would not be expected to increase, as would be the case with the ACE inhibitor. Perhaps more importantly, were direct renin inhibitors at least as effective as ACE inhibitors or ARB in terms of ameliorating atherosclerotic lesions, clinicians using these drugs and surely the manufacturer would be reassured.

Lu et al. addressed this issue by treating LDL receptor gene-deficient (Ldlr−/−) mice with aliskiren [4]. The adroit readership will be aware that renin–angiotensin systems are species specific. Why would aliskiren even work in the mouse? Wood et al. published the basic pharmacology of aliskiren [5]. They included data in their paper on the IC50 (50% inhibitory concentrations), a measurement of potency, enzyme specificity and species specificity of aliskiren in vitro. The aliskiren IC50 for human renin is 0.6 nM. For the rat, this value is 80 nM, and for the cat the value is 8000 nM. The IC50 value for mouse renin is not given in their paper. However, Lu et al. took care of measuring the IC50 [4]. They reported a value of 6 nM, which would imply that about a 10-fold increase in dose, compared to man, might do the trick. They show that at 50 mg/kg/day, Ang II and all breakdown products are markedly reduced. Furthermore, renin mRNA increased substantially, while the mRNAs of other components, such as ACE, ACE2, AT1 and AT2 receptors, were not affected. Cholesterol and aldosterone were not affected by aliskiren, although systolic blood pressure was modestly reduced. Interestingly, Ldlr−/− mice had a slight increase in blood pressure compared to controls in this study. Aliskiren eliminated this difference. Aliskiren dramatically reduced the atherosclerotic lesion size in a dose-dependent fashion in these experiments that were conducted over 12 weeks.

The macrophage is a pivotal cell in atherosclerotic plaque development, and innate immune mechanisms are important. Lu et al. next explored this issue [4]. They first checked if aliskiren treatment affected macrophage expression of 12/15 lipooxygenase protein or serum titres of autoantibodies against malondialdehyde-LDL. Both have been used as an index of atherosclerosis-related oxidant mechanisms. However, these parameters were not affected by aliskiren treatment. The authors next investigated the renin–angiotensin system in macrophages. Other cell types, such as cardiomyocytes, vascular smooth muscle cells and adipocytes, have been shown to harbour the components and to make angiotensin peptides. Lu et al. found that cultured macrophages expressed all components of the renin–angiotensin system and were able to produce...
Renin inhibition and atherosclerosis

Fig. 1. Aliskiren blocks formation of the decapptide angiotensin (Ang) I. Thus the octapeptide, Ang II will not be formed by angiotensin converting enzyme (ACE), aminopeptidases (AP) will not form Ang III, neutral endopeptidase (NEP) will not form Ang (1–7) that will not occupy its putative receptor Mas. The AT1 and AT2 receptors will be underemployed. Ang IV will not interact with the insulin-regulated aminopeptidase (IRAP). The importance of these breakdown products and putative signalling pathways remains unclear (adapted from [7]).

Angiotensinogen [4]. They next addressed the notion of renin in macrophages by bone marrow transplantation. Ldlr−/− mice received bone marrow (after having been irradiated) from renin−/− mice. Renin deficiency in bone marrow-derived cells not only ablated renin expression in these cells, but also markedly reduced atherosclerotic lesion area, when these Ldlr−/− mice were fed a high-fat diet. As a control, the authors repeated the bone marrow transplantation experiments using AT1 receptor-deficient bone marrow cells. However, the absence of the AT1 receptor in bone marrow had no effect on the atherosclerotic lesion size. Lu et al. also performed monocyte-adhesion studies to endothelial cells. Ang II increases monocyte adhesion, an effect that can be blocked with ARB treatment. Renin deficiency in bone marrow-derived cells also markedly reduced adhesion to endothelial cells. Macrophages (Greek: ‘big eaters’, from makros ‘large’ + phagein ‘eat’) are cells within the tissues that originate from monocytes. Thus, we can conclude that renin plays a role in stimulating the big eaters. Aliskiren appears to curb their appetites.

What are the clinical implications of these findings? We can probably rest assured that aliskiren will function equally well as ACE inhibitors or ARB in terms of atherosclerosis protection, although statins are far more important in that regard and the outcomes of hard endpoint studies with aliskiren are not yet available. We can probably put to rest theories regarding the importance of other angiotensin breakdown products, Ac-SDKP, bradykinin and the AT2 or Mas receptors in terms of atherosclerosis protection. More important in my view is the notion of macrophage participation and a cell-based renin–angiotensin system in atherosclerosis. Macrophages without renin or with renin inhibition protected from plaque development and expansion. Macrophages without the AT1A receptor did not.

As mentioned earlier, Cassis, Daugherty and associates, the same investigators responsible for the aliskiren paper discussed here, showed previously that Ang II infusion into Ldlr−/− mice accelerates atherosclerosis and promotes formation of abdominal aortic aneurysms [3]. In an earlier study, they checked whether or not Ang II interacts with AT1 receptors on infiltrating macrophages versus resident vascular cells [6]. In that study, male Ldlr−/− mice, which were either AT1A receptor +/+ or −/−, were fed a fat-enriched diet and infused with either saline or Ang II. The authors found that Ang II-induced augmentation of atherosclerosis and aneurysm formation was ablated in AT1A receptor −/− mice. They then performed bone marrow transplantation studies to determine the role of AT1a receptors expressed on infiltrating cells. AT1a receptor +/+ and −/− mice were irradiated and repopulated with bone marrow-derived stem cells of either genotype. These four groups of chimeric mice were then infused with either saline or Ang II. Repopulation of irradiated AT1a receptor +/+ mice with −/− bone marrow-derived cells resulted in only modest reductions in Ang II-induced atherosclerosis. Unexpectedly, AT1a receptor-deficient recipient mice were dramatically protected from Ang II-induced vascular pathologies, irrespective of donor genotype. The authors concluded that the presence of the AT1A receptor in resident tissue (like endothelial and vascular smooth muscle cells) was required for the initiation of Ang II-induced atherosclerosis and aneurysm formation. Thus, it appears that renin in the macrophages and AT1 receptors in the resident cells are pivotal to atherosclerosis progression.

Clinical perspective

Ldlr−/− and Apoe−/− mice are contrived models of homozygous familial hypercholesterolaemia; they have little if any relevance to human atherosclerosis. The mice show that Ang II plays a role in the atherogenic process and that all three currently used clinical strategies of ACE inhibition, ARB or direct renin inhibition are effective in countering the Ang II-related atherogenic effects in these models. Should patients with atherosclerosis (who do not invariably have elevated LDL levels) routinely receive renin–angiotensin-system-inhibiting drugs? Clinical trials are necessary to answer this question. The author might answer the question with: ‘Yes, but only after they have stopped smoking, have normal blood pressures and blood sugars, and are taking their statin’.

Conflict of interest statement. The author has received research grants-in-aid from Novartis. He is a member of the Renin Academy and has lectured on direct renin inhibition.

References


Received for publication: 10.3.08
Accepted in revised form: 10.3.08