Renin inhibition and atherosclerosis*

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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 intensely 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 (Ac-SDKP), 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, Ac-SDKP 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 lipoxygenase 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...
The 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’.

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References


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