A recent analysis of the Framingham Heart Study implicated elevated serum aldosterone as an independent risk factor for the development of cardiovascular disease. Although adrenal-derived aldosterone may prove to be important in this regard, less evident is the source of aldosterone and the mechanism for mineralocorticoid receptor (MR) activation in studies such as the Randomized ALdactone Evaluation Study (RALES) and the Eplerenone Post-acute myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS), where MR blockade exerts obvious cardiovascular benefit but adrenal aldosterone levels are normal. In this issue of Hypertension, the article by Takai et al documents such a study and thereby adds to the discussion not only of the applicability of MR blockade in cardiovascular disease but also of the mechanisms for MR activation. The authors report that monkeys with diet-induced hypercholesterolemia treated with the selective MR antagonist eplerenone had reduced extent of atherosclerotic lesions in aorta and carotid arteries compared with placebo-treated monkeys. The results extend the beneficial influence of MR blockade to a model with similarities highly relevant to the atherogenic process in humans.

Rajagopalan et al were the first to demonstrate that local vascular expression of MR might play a role in atherosclerosis. In this study, dietary hypercholesterolemia in rabbits was associated with increased aorta superoxide generation. Eplerenone administration to hypercholesterolemic rabbits normalized superoxide generation, decreased NADH and NADPH oxidase activity to basal levels, and nearly normalized endothelial-dependent vasorelaxation. A study by Keidar et al showed similar inhibition of atherosclerosis when eplerenone was administered to apolipoprotein E (apoE)-deficient mice. As in rabbits, eplerenone reduced markers of oxidative stress, including the ability of macrophages to oxidize LDL, macrophage superoxide anion release, and the susceptibility of LDL to oxidation. It is worth noting that in each of these models, plasma aldosterone levels were unaltered by hypercholesterolemia. This observation does not imply that aldosterone is without proatherogenic properties, because its infusion exacerbated the development of naturally occurring atherosclerosis in apoE-deficient mice. Rather, the lack of elevated adrenal aldosterone raises questions as to how MR activation takes place in the context of hypercholesterolemia. It is appropriate to ask at this point if the effects ameliorated by MR blockade are mediated exclusively by adrenal aldosterone, if aldosterone synthesis occurs within vascular tissues and exerts autocrine/paracrine effects, and if the effects of MR blockade are primarily related to aldosterone interaction or may be nonsteroidal in nature and include other mechanisms, such as those mediated by reactive oxygen species and angiotensin II (Ang II).

Consideration of potential pathways for MR-regulated atherogenesis incorporates several lines of reasoning. First, increased adrenal aldosterone secretion reflected by increased serum or plasma levels may not be necessary to promote atherosclerosis if vascular MR receptor density is increased by hypercholesterolemia. Yoshida et al evaluated MR mRNA and protein in tissues taken from the left ventricle of normal and failing human hearts and determined that MR expression was comparatively increased in the failing hearts. Whether a similar increase in MR takes place in atherosclerotic lesions of monkeys was not reported by Takai et al, nor have other studies established a connection between hypercholesterolemia and vascular MR density. Although MR mRNA was detected in both normocholesterolemic and hypercholesterolemic rabbit aortas in the study by Rajagopalan et al, the numbers of animals in the study were too few to evaluate whether hypercholesterolemia altered MR expression. Jaffe and Mendelsohn detected MR mRNA and protein in both human coronary and aortic vascular smooth muscle cells (VSMCs) and determined that activation of MR in VSMCs mediates aldosterone-dependent gene expression. Evaluation of possible hypercholesterolemia-induced vascular MR expression is important to understanding the vascular benefits of MR blockade, just as the determination that increased vascular Ang II type 1 (AT1) receptor density accompanies hypercholesterolemia firmly established Ang II as a proatherogenic factor. It is certainly possible that increased vascular MR density is a mechanistically relevant explanation for aldosterone-mediated atherogenesis because each of the principle cell types that constitute hypercholesterolemia-induced atherosclerotic lesions express MR.

On the other hand, a second, more complex answer might be that the enzymatic pathways necessary for mineralocorticoid production are present in atherosclerosis-prone vasculature and that some component of hypercholesterolemia stimulates local steroidogenesis to produce aldosterone. In support of this notion, mRNAs encoding all steroidogenic enzymes necessary to synthesize aldosterone were detected in human aorta. Locally produced aldosterone may interact...
with vascular MRs, resulting in vascular oxidative stress and potentiation of the atherosclerotic process. Aldosterone stimulation of angiotensin-converting enzyme mRNA and activity in VSMCs is inhibited by MR blockade, and aldosterone may also increase vascular AT₁ receptors,7 thus amplifying the Ang II contribution to atherogenesis. Conversely, the inhibitory effect of AT₁ receptor blockade on atherosclerosis may be partially achieved by reducing AT₁ receptor–mediated vascular aldosterone synthase activation and the local production of aldosterone. In this way, eplerenone may either act to inhibit atherogenesis by directly blocking aldosterone-stimulated, MR-mediated pathways or by suppressing local Ang II production. This autocrine/paracrine paradigm is supported by studies demonstrating de novo synthesis of aldosterone in myocardium and cardiac vasculature under appropriate, and typically injury-related, conditions. A number of studies support steroidogenesis by endothelial cells and VSMCs, whereas a similar number dispute these findings. For example, in a very recent study in human coronary VSMCs,9 aldosterone synthase mRNA or protein and aldosterone release in response to Ang II were not detected. To answer whether aldosterone is synthesized in atherosclerotic lesions, it is necessary to determine whether the enzymes required for aldosterone biosynthesis are expressed in these lesions and if increased concentrations of aldosterone are present within the lesions compared with the circulation.

A third possible explanation for MR blocker–mediated inhibition of atherosclerosis is the potential independent activation of MR by Ang II. The study by Jaffe and Mendelsohn8 revealed an aldosterone-independent, AT₁ receptor–mediated MR activation in human coronary VSMCs. They found that Ang II stimulated nuclear localization of MR and that spironolactone as well as AT₁ receptor blockade inhibited Ang II–mediated gene expression. A clue as to whether similar Ang II–mediated MR activation may be functional in atherogenesis is found in the Takai et al study, where the reduction in atherosclerosis lesions in aorta with eplerenone treatment was considerably less than that previously reported by these investigators11 in the same nonhuman primate model following AT₁ receptor blockade. In the absence of elevated adrenal aldosterone, the antiatherosclerotic effects of eplerenone could be attributed in part to its ability to neutralize AT₁ receptor–mediated responses because Ang II and AT₁ receptors are increased in atherosclerotic lesions. However, Cassis et al12 showed that MR blockade with spironolactone had no effect on Ang II–induced atherosclerosis in apoe-deficient mice, indicating that aldosterone is not a major mediator of Ang II–induced atherosclerosis and suggesting that Ang II activation of MR is also not a major pathway for atherogenesis.

A fourth and novel hypothesis for nonaldosterone MR activation that may be important in atherosclerosis was recently proposed. Funder13 suggested that MR may be activated not only by aldosterone, but also independently by the local generation of reactive oxygen species inherent to atherosclerotic lesions and then by normal levels of plasma cortisol. This enticing prospect does not require elevated aldosterone or Ang II–mediated effects because MR would be driven directly within the vascular wall by inflammation. Final resolution of the role of MR blockade in atherogenesis will require additional studies in which MR kinetics and aldosterone synthase expression in atherosclerotic lesions are determined. Regardless, the positive results of the study by Takai et al should encourage investigation of whether atherosclerosis inhibition by MR blockade added to angiotensin-converting enzyme inhibition is superlative to monotherapy.

References


Eplerenone Antagonizes Atherosclerosis, But What Is the Agonist?
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