The Mineralocorticoid Receptor in Heart
Different Effects in Different Cells

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The mineralocorticoid receptor (MR) antagonists (MRAs) spironolactone and eplerenone have beneficial effects in patients with heart failure (HF) or left ventricular dysfunction. This underscores the major role of an inadequate hormonal stimulation leading to MR activation in HF. However, the actions of MRAs are complex and several questions remained unsolved. Which biochemical pathways are activated by the hormone that binds the cardiac MR? Which hormone binds the cardiac MR? In which pathological settings are the MRAs most appropriately used?

The MR is the intracellular receptor of aldosterone. The hormone-receptor complex binds to a specific DNA sequence and triggers the transcription of target genes. In epithelial cells, the induced genes are mostly involved in the control of sodium reabsorption. However, the link between the beneficial effects of MRA in HF and these actions related to sodium control are unclear. Spironolactone is efficient in HF patients at a subhypertensive dose that likely did not involve diuretic effects. This suggests that spironolactone action in this setting was, at least in part, directed toward the MR of nonepithelial cells.

Disappropriately increased levels of aldosterone in plasma are associated with inflammation and fibrosis in heart and blood vessels. Indeed, improved outcomes with spironolactone in HF have been linked to the antifibrotic effects of spironolactone. The MR is expressed in several cardiac cell types, cardiomyocytes and fibroblasts, and in vascular endothelial and smooth muscle cells, raising the question of its function in these tissues. Genetic technologies in mice have allowed selective deletion or overexpression of MR in different cardiac cell types. These tricky experiments give novel and interesting informations.

The study published in this issue of Hypertension by Lother et al² compared the response to a chronic severe pressure overload in 2 mouse models with cell-specific deletion of MR in cardiomyocytes or in fibroblasts. They observed that MR deletion in cardiomyocytes prevented the left ventricular dilatation and failure observed in control mice after pressure overload. Left ventricular inner diastolic diameter and wall tension increased in control mice after pressure overload but remained unchanged in mice with cardiomyocyte MR deletion. This is consistent with previous results showing that eplerenone delayed the transition from compensated cardiac hypertrophy to dilatation and failure in mice.³ Similarly, neither eplerenone¹ nor cardiomyocyte-specific MR ablation in the study by Lother et al² prevented cardiac hypertrophy after pressure overload.

The results of this loss-of-function experiment may be compared with the mirror experiment, the effect of MR gain of function. The conditional MR-specific overexpression in cardiomyocytes induces a cardiac ion channel remodeling, severe ventricular arrhythmias, and a high rate of death.⁴ This finding is possibly related to the increased rate of atrial fibrillation found in patients with hyperaldosteronism.⁵ More surprising at first glance is the response to aortic constriction of mice with MR deletion in fibroblasts: they are not protected from the cardiac fibrosis, which is observed in control mice.² However, this observation is consistent with findings from macrophage-specific MR deletion studies. Indeed, MR deletion in macrophages reduced cardiac oxidative stress and inflammation, as well as cardiac fibrosis induced by Nω-nitro-L-arginine methyl ester/angiotensin II or deoxycorticosterone acetate/salt treatment.⁷ Importantly, these inflammatory-type cells express the MR and are almost never found in normal hearts. However, a severe vascular stress triggers the release of cytokines like monocyte chemoattractant protein 1 that induce the infiltration of macrophages in the heart. In these experiments, MR knockout in macrophages prevented the cardiac fibrosis, although the cardiac recruitment of these cells was not prevented.⁶–⁷ These observations indicate that an MR signaling in macrophages is required to elicit the cardiac fibrosis associated with severe hemodynamic or hormonal challenges, and that it is mainly of extracardiac origin. This is in agreement with other results where cardiomyocyte-specific MR deletion² or overexpression⁴ did not induce fibrosis.

Now, the scheme becomes more clear (Figure). There are (at least) 2 major functional pathways that may be activated by the MR, depending on the cell type that bears MR. The perivascular inflammatory phenotype that is seen in conditions of severe hemodynamic or hormonal stress is of vascular origin, and it is secondary to the activation and cardiac infiltration of macrophages. The macrophage MR thus plays a prominent role in cardiac fibrosis. On the other hand, the MR of cardiomyocytes serves functions that are specifically related to the properties of the cardiac muscle but not to the cardiac hypertrophic response. The globally negative effects that result from MR activation in cardiomyocytes remain an open question: why should such a harmful receptor be present in heart? One may hypothesize that
Cardiac expression of MR is increased in hypertension, atrial fibrillation, myocardial infarction, and diastolic HF. Therefore, the MR activation level could be increased even with normal levels of aldosterone and glucocorticoids. Moreover, an aldosterone-independent activation of the MR is another intriguing possibility. This is suggested by observations in the kidney, where the MR may be activated by rac-1 in the absence of aldosterone, and by a previous observation that MR is activated by angiotensin II in cultured smooth muscle cells. Indeed, angiotensin II and aldosterone are chronically increased in cardiovascular diseases. Cross-talks exist between the pathways of angiotensin and aldosterone that may potentiate their own actions. These effects deserve additional studies and support the concept of a combined inhibition of an angiotensin receptor and MR in cardiovascular disease. MRAs are underused in HF, and the recent results discussed above suggest that MRAs should be more widely used to antagonize the increased MR activation seen in several pathologies, including HF.

Sources of Funding

This work was supported by Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, and Fondation de France.

Disclosures

None.

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Hypertension. 2011;57:679-680; originally published online February 14, 2011;
doi: 10.1161/HYPERTENSIONAHA.110.164962
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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