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Mineralocorticoid Receptors, Corticosteroids and the Heart.

Where do we stand?

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For heart failure, the clinical usefulness of mineralocorticoid receptor (MR) blockers is remarkable. Following 24 months of treatment, there was a 30% reduction in the risk of death and hospitalization in the spironolactone group as compared to placebo in left ventricular systolic dysfunction heart failure patients primarily in Class III and IV of the NY Heart Association Functional Class, who were already on standard therapy including angiotensin converting enzyme (ACE) inhibitors [1]. Eplerenone, another MR antagonist, was effective at decreasing the risk of death after acute myocardial infarction (MI) [2]. Further, spironolactone was also effective at decreasing the ventricular remodeling and collagen formation in the acute phase of MI [3]. It was initially believed that aldosterone was involved in heart failure only through increasing sodium retention and potassium loss. However, as the aforementioned study suggests, it is now appreciated that aldosterone also causes myocardial and vascular fibrosis [4].

Insight into the exact mechanisms underlying the incredible cardiac improvement with MR blockers is still needed. One of the reasons this remains elusive is that MR signaling is considerably complex. Aldosterone is the primary mineralocorticoid binding to MR. However, corticosteroids also bind to MR with equivalent or higher affinity [5]. Binding of both ligands elicits genomic and non-genomic signaling. Depending on the ligand, there is differential activation of signaling pathways with unique consequences [6]. Aldosterone dissociates more slowly and induces greater transcriptional activity than cortisol at any given concentration [6]. In animal models, cardiac-specific deletion of the murine MR protected against progressive adverse cardiac remodeling and molecular alterations in MI [7]. However, it was also found that macrophage-specific deletion of MR prevented chronic mineralocorticoid/salt-induced cardiac fibrosis and increased systolic blood pressure in rats [8] suggesting that multiple different cell types contribute.

Properties of the ligand binding to MR contribute further to the complexity. Recent evidence supports the possibility of heterodimerization of mineralocorticoids and corticosteroids binding to MR suggesting both may be critical for optimal functioning at least in some cells [9]. The relative abundance of corticosteroids to mineralocorticoids is astounding and even if bound inactive corticosteroids are discounted, corticosteroids are still in 10 to 100-fold abundance [5]. The enzyme 11 β -hydroxysteroid dehydrogenase (11 β HSD2) converts cortisol and corticosterone to inactive MR congeners thus further decreasing the relative abundance of non-mineralocorticoid ligand for MR but this requires tissue specific expression of 11 β HSD2 [5]. To date, studies have suggested that 11 β HSD2 is not expressed in cardiac myocytes thus meaning corticosteroids are free to bind MR [6]. Also adding to the intricacy, recent data suggests spironolactone may be acting as an inverse agonist exerting at

least some of its positive effects towards cardiac function through that mechanism [10]. For example, spironolactone alone decreased cardiac infarct size in a rat model of MI [11]. This benefit was maintained in adrenalectomized animals suggesting at least part of the mechanism of the protective effect of spironolactone is direct and not through corticosteroids [11]. Therefore, a clear understanding of the role of MR and its ligand binding properties in cardiovascular physiology and pathophysiology is still lacking. Some of this is related to the complexity of the cardiovascular system being an integration of heart, blood vessels, kidney, brain, nervous system, immune system etc. and some is related to in vitro versus in vivo investigation.

In this issue of Journal of Hypertension, Chai et al. attempt to address some of the controversies surrounding mineralocorticoid versus corticosteroid/glucocorticoid action at MRs using an in situ isolated Langendorff heart perfusion approach [12]. Not only do they consider the activity at MRs under normal baseline conditions, they also examine the effects under pathological conditions. Another study by Mihailidou et al. also took a somewhat reductionist approach [11]. Both these studies are comparable in that they use isolated hearts perfused with cell-free medium therefore there is no immune cell response and as mentioned above, macrophage MRs likely play an important role [11,12]. However, they allow for investigation in isolation of other parameters such as the effects of the inhibitors/agonists on blood pressure or kidney function. Importantly, the results from both studies are somewhat limited since they are neither in vivo nor in vitro. Neither study examined cell-type specific responses. There is likely subtle regulatory control of the MR system and considering the heart en masse may preclude deciphering these differences. Understanding the role of MRs in each of the cardiac cell types including cardiac myocytes, fibroblasts, endothelial cells, or vascular smooth muscle cells will be critical to fully understanding MR action. Further, each study measured different end-points. Mihailidou et al. do not address function but rather focus on infarct size [11]. In the current study, they measure left ventricular pressure and coronary flow. Neither are excellent indices of cardiac function but they are an initial attempt at examining the extent that corticosteroids act at MR to affect cardiac function under disease conditions [12].

Chai et al provide evidence to support that the isolated, intact heart is incapable of synthesizing glucocorticoids de novo under normal or pathological conditions [12]. This is important as it has been suggested as a further argument to support corticosteroids acting at MRs in the heart. Others have also shown this to be true for aldosterone [13,14]. Therefore, current data suggests that any cardiac MR or glucocorticoid receptor activation occurs because of ligands present within the plasma.

Chai et al have attempted to address whether corticosteroids act at MR in the heart under normal and pathological conditions [12]. Using various antagonists and agonists, the authors conclude that cardiac effects are unique through the MR and glucocorticoid receptor. Aldosterone increased left ventricular pressure with no change in coronary flow whereas corticosteroid increased both left ventricular pressure and coronary flow. Corticosteroid effects were fully blocked by RU486, a glucocorticoid receptor antagonist, but not an inhibitor of MR or 11 β HSD2. Therefore, at least with respect to the endpoints measured in the isolated heart, corticosteroids are not acting via MR. Whether complexities that have been shown in vitro such as heterodimerization occur in this in situ or in an in vivo setting remains to be determined. It also remains to be determined the extent to which interaction with other receptors such as the angiotensin AT1 receptor plays a role in ligand specificity at the MR [15,16] and it is important to point out that successful clinical trials have had at least one inhibitor of the renin-angiotensin system on board in addition to the spironolactone.

It appears that, at least under normal baseline conditions, 11 β HSD2 is not a likely candidate for converting active corticosteroid into the inactive form [6,12]. However, data derived by Chai et al. challenge this notion and suggest that 11 β HSD2 expression in the left ventricle may be increased under disease conditions such as hypertrophic cardiomyopathy [12]. Further, their data suggest there is an increase in MR mRNA expression thereby increasing the potential for aldosterone to bind, and corticosteroids to be inactive, at the MR. Aldosterone appears to mediate mostly adverse events in the heart and increasing aldosterone signaling potential would exacerbate this. This enhancement in signaling during disease conditions may help to explain the effectiveness of MR inhibition. Perhaps, an increase in MR expression and an increase in 11 β HSD2 further enhances the beneficial effects of spironolactone not only through inhibition of the negative effects of aldosterone on cardiac function but also by increasing the potential of the beneficial effects of spironolactone acting as an inverse agonist although this remains to be determined [5,11].

The current findings by Chai et al. [12] clearly illustrate that the heart does not possess steroidogenic capacity. Further their data suggest that MR signaling capacity has the potential to change under disease conditions. Their data suggest that in the isolated heart, measuring the endpoints they measured, glucocorticoids do not act through MR but it remains to be determined whether this is the case in vivo when there is circulating plasma levels of both ligands and other known or unknown cofactors. Therefore, this study may provide some insight into the mechanisms underlying the success of MR inhibition for heart failure but further studies are required to convincingly understand the complexities of glucocorticoid and mineralocorticoid receptor activation in heart failure.

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