Aldosterone and Mineralocorticoid Receptor Signaling as Determinants of Cardiovascular and Renal Injury: From Hans Selye to the Present

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Keywords

Mineralocorticoid receptor antagonists · Aldosterone · Cardiovascular · Renal

Abstract

Background: A full understanding of the mechanisms of action of aldosterone and its interaction with the mineralocorticoid receptor (MR) allows a theoretical framework to predict the therapeutic potential of MR antagonists (MRAs) in CKD, and heart failure with reduced ejection fraction. **Summary:** The initial focus on the mechanisms of action of aldosterone was directed primarily on its role in modulating renal excretory function. In contrast, many recent studies have demonstrated a wider and expanded role for aldosterone in modulating inflammation, collagen formation, fibrosis, and necrosis. Increasing evidence has accrued that implicates the pathophysiological overactivation of the MR as a major determinant of progression of CKD. By promoting inflammation and fibrosis, MR overactivation constitutes a pivotal determinant of CKD progression and its associated morbidity and mortality. In accord with this mechanism of action, blockade of the MR is currently being investigated as a novel treatment regimen to slow the progression of CKD. The recently reported FIDELIO-DKD (Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease) study demonstrated that patients with CKD and type 2 diabetes who were treated with finerenone (a novel nonsteroidal MRA) manifested a lower risk of a composite primary

outcome event compared with patients in the placebo arm (defined as kidney failure, or a sustained decrease of $\geq 40\%$ in the estimated glomerular filtration rate from baseline, or death from renal causes). In addition, patients in the finerenone group also manifested a lower risk of a key secondary outcome event (defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). **Key Messages:** Based on the success of the FIDELIO-DKD study, future studies should be implemented testing the hypothesis that a wide array of nondiabetic CKD is modulated by overactivation of the MR, and consequently may be amenable to treatment with novel nonsteroidal MRAs. Future studies are encouraged to elucidate the clinical implications of the interplay of nonsteroidal MRAs and the components of the renin-angiotensin cascade. The unique and recently reported interrelationship of fibroblast growth factor (FGF23) and aldosterone may also constitute a propitious subject for future investigation.

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Introduction

The oft-repeated metaphor, “If I have seen further, it is by standing on the shoulders of giants,” is attributed to Isaac Newton [1]. This concept conveys the meaning of discovering truth by building on the previous discoveries. This axiom clearly describes the scientific trajectories that resulted in the discovery of aldosterone and the elucidation

tion of mineralocorticoid-induced inflammation, fibrosis, and cardiovascular remodeling.

Although many readers will date the birth of aldosterone to 1953, when Simpson and Tait developed a high-sensitivity bioassay allowing characterization of mineralocorticoid activity, there were earlier inklings that foreshadowed this feat. As early as 1950, Quentin Deming and his mentor, John Luetscher, one of the giants of medicine, reported increased sodium retention in patients with heart diseases compared with healthy subjects [2]. Three years later, Simpson et al. [3] managed to purify just a few milligrams of aldosterone, then known as electrocortin, from beef adrenal glands. The structure of aldosterone was established shortly thereafter [4], paving the way for inventions of novel assays, including the double isotope derivative assay developed by Kliman and Peterson [5]. Subsequent sequential investigations of the mechanisms of action of aldosterone demonstrated its regulatory role in extracellular volume homeostasis and in subserving blood pressure (BP) through its effects on potassium excretion and sodium retention [6].

How the Role of Aldosterone Has Expanded Markedly in the Past 30 Years: A Dramatic Paradigm Shift

In an eloquent review published 10 years ago, Funder [7] summarized the dramatic change in our prevailing view of aldosterone and the mineralocorticoid receptor (MR) over the past 30 years. As Funder noted, “Over the more than 5 decades since its characterization in 1953, aldosterone has been something of an orphan hormone, foster-parented by physiologists, endocrinologists, nephrologists, pharmacologists, and, most recently, cardiologists.” In 2021, one can unequivocally state that aldosterone is no longer an orphan hormone, but rather a prized focus of basic and clinical research. As Funder wrote in 2010, a summary of the understanding of the interaction between aldosterone and the MR in 1990 was that (a) angiotensin was the major determinant of aldosterone secretion, (b) aldosterone was the sole physiologic ligand for MR, (c) aldosterone elevated BP primarily by its sodium-retaining effects leading to volume expansion, (d) MR antagonists (MRAs) acted by blocking the binding of aldosterone to MR, and that (e) aldosterone acted genomically and nongenomically. After 30 years, we now know that the majority of these concepts are wrong [8, 9]. It is now accepted that (a) angiotensin does not constitute the major driver of aldosterone secretion, (b) aldosterone

is only one of the physiological ligands for MR, and (c) aldosterone raises BP primarily by actions on the vasculature and central nervous system although aldosterone’s sodium-retaining effects are relevant in defending volume homeostasis in the setting of hypovolemia.

A more complete understanding of aldosterone’s true role constitutes a rational framework for examining the therapeutic potential of MRAs in hypertension and CKD. An understanding of the complex interplay between aldosterone and the MR is necessary to obtain this framework.

Renal Effects of Aldosterone

The steroid aldosterone is the main mineralocorticoid hormone; it is synthesized in response to hyperkalemia or sodium depletion, in the glomerular zone of the adrenal cortex, as the endpoint of activation of the renin-angiotensin system [10]. Further studies have shown local aldosterone production in peripheral tissue [11, 12]. Aldosterone plays a major role in the control of both BP and extracellular volume homeostasis by stimulating renal sodium reabsorption and potassium excretion [6]. The full pathway of aldosterone’s action will not be described but several comprehensive reviews are published [10, 13–15].

Extrarenal Effects of Aldosterone: Early Studies Portending Mineralocorticoid-Induced Inflammation, Fibrosis, and Cardiovascular Remodeling

A series of parallel studies indicated a wider, nonepithelial role for aldosterone in promoting inflammation, collagen formation, fibrosis, and necrosis. In 1943, Selye et al. [16, 17] carried out keynote experiments proving the central importance of MR agonists on organ damage. They demonstrated that the administration of salt and deoxycorticosterone acetate (aldosterone was unavailable at the time) produced malignant hypertension, which, importantly, was associated with inflammation and fibrosis in various organs (i.e., malignant nephrosclerosis, cardiac hypertrophy, and a rigid aorta) [18]. Selye [19] termed “a state of chronic stress” that manifested in the coronary, renal, and systemic vasculature as the formation of perivascular granulomas. These vascular abnormalities preceded myocardial necrosis and fibrosis [20].

Unfortunately, these observations were forgotten for over 40 years, but in retrospect, it is apparent that they constituted the foundation for future investigations that

defined the nonepithelial effects of aldosterone. After a 40-year gap, Weber and colleagues [21] rediscovered these effects, demonstrating that chronically elevated aldosterone, when coupled with salt loading, promoted cardiac fibrosis [22]. By contrast, spironolactone, an aldosterone receptor antagonist, conferred a protective effect against the development of cardiac fibrosis when given to uninephrectomized rats receiving a high salt diet and aldosterone. In concert, this evidence suggested that cardiac fibrosis could be mediated by MR activity.

MR Overactivation as a Determinant of CKD Progression

Over two decades ago, Epstein published an in-depth review marshalling evidence that selective blockade of aldosterone, independent of renin-angiotensin blockade, reduces proteinuria and nephrosclerosis in the spontaneously hypertensive stroke-prone rat model and reduces proteinuria and glomerulosclerosis in the subtotaly nephrectomized rat model (i.e., remnant kidney) [23]. Furthermore, selective reinfusion of aldosterone restores these abnormalities despite continued and sustained renin-angiotensin blockade. Subsequently, increasing evidence implicated pathophysiological overactivation of the MR as a determinant of progression of CKD and its associated morbidity via a mechanism to promote inflammation and fibrosis. This formulation provides a rationale for investigating blockade of the MR as a novel treatment approach to retard the progression of CKD [24, 25].

The steroidal hormones that activate the MR – aldosterone and cortisol – are well known. Spironolactone and eplerenone, the approved steroidal MRAs, reduce both mortality and hospitalization when treating heart failure [26, 27]. Although there have been no long-term studies on whether they can reduce the rate of progression of CKD [28], a few short-duration clinical trials with MRAs have been conducted. As I have discussed in an in-depth review, the Aldosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST trial) (spironolactone 25 mg/day, NCT01848639) [29] is ongoing, and the PHASE study (Eplerenone in Hemodialysis Trial) (NCT01650012) [30], a pilot, randomized, double-blind, clinical trial studying eplerenone (50 mg/day) has concluded [28]. In contrast, the novel nonsteroidal MRA finerenone has recently been shown to slow progression of CKD [31]. To understand these clinical differences, it is important to understand the differences between the steroidal MRAs and nonsteroidal MRAs, such as finerenone.

Comparison between Nonsteroidal MR Antagonist (Finerenone) and Steroidal MR Antagonists

As detailed in a recent scholarly review, there are many distinct differences between the nonsteroidal MRA (finerenone) and steroidal MRAs (spironolactone and eplerenone) [25]. They differ with respect to the mode of MR antagonism, tissue distribution, pharmacokinetics, effects on cofactor recruitment, and effects on inflammation and fibrosis in rodent models of cardiac fibrosis and CKD. For the purposes of the present review, 3 attributes will be highlighted:

1. Pharmacokinetics: Finerenone has no active metabolites and a short half-life. In contrast, spironolactone is a prodrug with multiple active metabolites with long half-lives. Eplerenone has no active metabolites but has a half-life of 4–6 h
2. Effect on inflammation and fibrosis: Finerenone (at equi-natriuretic doses to eplerenone) manifests strong inhibition of inflammation and fibrosis
3. Effect on cofactor recruitment in the absence of aldosterone in vitro: Finerenone acts as an inverse agonist (inhibits cofactor binding in the absence of aldosterone). In contrast, both spironolactone and eplerenone act as partial agonists for cofactor recruitment (see Fig. 1)

The Hierarchy of Evidence from the Laboratory to FIDELIO-DKD and FIGARO-DKD

Finerenone is a novel, nonsteroidal, selective MRA that has a high affinity for the MR and a unique binding mode that has been demonstrated to reduce inflammation and fibrosis in animal models [25, 32–35]. In Phase II clinical trials, finerenone produced significant reductions in albuminuria. Concomitantly, the finerenone-associated adverse events were similar to those observed in the placebo cohort, and there was less hyperkalemia compared with spironolactone [36]. Based on the success of the Phase II studies, ARTS-HF (MR Antagonist Tolerability Study-Heart Failure) (NCT01807221) [37] and ARTS-DN (MR Antagonist Tolerability Study-Diabetic Nephropathy) (NCT01874431) [36], and the biological plausibility of cardiorenal benefit, 2 Phase III clinical trials, the Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in reducing cardiovascular mortality and morbidity in Diabetic Kidney Disease (FIGARO-DKD) studies were initiated in 2015. The rationale of the trials was to

Fig. 1. Finerenone reduces cofactor recruitment to the MR, thereby reducing downstream expression of pro-inflammatory and pro-fibrotic factors following MR overactivation. Reproduced with permission of Agarwal et al. *Eur Heart J*. 2021;42(2):152–61. MR, mineralocorticoid receptor.

demonstrate and consequently provide new treatment opportunities for improving cardiorenal outcomes in patients with CKD in type 2 diabetes (T2D).

The results of the FIDELIO-DKD study were presented at the recent 2020 American Society of Nephrology Annual Meeting and simultaneously published in the

New England Journal of Medicine [31, 38]. In brief, patients with CKD and T2D who were treated with finerenone manifested a lower risk of a primary outcome event (defined as kidney failure, or a sustained decrease of $\geq 40\%$ in the estimated glomerular filtration rate from baseline, or death from renal causes) than patients in the compara-

tor placebo arm (21.1 vs. 17.8%, HR 0.82, 95% CI 0.73–0.93, $p = 0.001$). In addition to the primary endpoints, patients in the finerenone group also manifested a lower risk of a key secondary outcome event (defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) [31].

The results of FIDELIO-DKD suggest that in patients with CKD and T2D, finerenone constitutes an effective treatment for kidney and cardiovascular protection. The significance of the observed benefits of finerenone is highlighted by considering the context in which the study was conducted. In contrast to many earlier renal protection trials, wherein guideline-mandated renin-angiotensin-aldosterone system (RAAS) inhibitor therapy fell short, the results in the FIDELIO-DKD clinical trial were obtained on a background of guideline-directed RAAS blockade that achieved a maximum labeled dose that did not cause unacceptable side effects, plus well-controlled glycated hemoglobin and BP levels, thereby elevating the hurdles that needed to be cleared to meet the predefined endpoints.

Finally, the results should be interpreted considering the patient population with multiple coexisting conditions and advanced CKD, who consequently were at high risk for both kidney and cardiovascular events. Furthermore, the benefits of finerenone were observed early: after 12 months for the kidney outcome and as early as 1 month for the cardiovascular outcome, and these benefits were sustained throughout the extended duration of the trial.

Considerations for the Future

Reawakenings: Updating Established Paradigms in Physiology, Pathophysiology, and Clinical Science

In addition to demonstrating that finerenone constitutes an effective treatment for kidney and cardiovascular protection in patients with T2D, I propose that nonsteroidal MRAs could be implemented in an array of future clinical trials. In the final section of this paper, I will delineate several potential investigations of interest.

CKD of Diverse Etiology

Whereas many of the recent clinical sodium-glucose cotransporter-2 inhibitor (SGLT-2i) clinical trials and FIDELIO-DKD have focused on patients with T2D and associated CKD and/or heart failure with reduced ejection fraction (HFrEF), additional expanded indications beckon. There are many underserved clinical cohorts. An ex-

ample that I believe should be considered is sickle cell nephropathy. Sickle cell disease (SCD; hemoglobin SS, hemoglobin SC, and hemoglobin S/beta-thalassemia genotypes) is one of the most common monogenic diseases with over 300,000 affected births worldwide. Millions of people around the world live with SCD. Over 40 years ago, less than half of children born with SCA were expected to reach adulthood [39, 40]. A wide array of treatment advances, including hydroxyurea as a disease-modifying therapy for SCD, and treatment strategies for primary and secondary stroke prevention have succeeded in extending survival of children with SCD [41]. Approximately, a third of adults with SCD develop CKD, and a significant proportion of these patients progress to end-stage renal disease [42, 43]. Patients with SCD-associated kidney failure have high mortality [44]. Whereas renal replacement therapy with hemodialysis can extend survival, the start of dialysis per se is a poor prognostic factor with 1-year mortality of 26% [45]. Patients with SCD-associated kidney failure are less likely to receive transplantation, even after waitlist registration [44]. Because conventional renal replacement treatment modalities for SCD-associated kidney failure are wanting, newly available treatment modalities should be considered and clinical investigations implemented. Because theoretical considerations indicate that inflammation and fibrosis are mechanisms that mediate sickle cell nephropathy; therefore, this patient cohort should benefit from treatment with a nonsteroidal MRA.

The Interplay of the MR with Components of the Renin-Angiotensin Cascade, a Mediator of Cardiorenal Inflammation and Necrosis

As detailed in a recent review [28], there are multiple mechanisms that participate in aldosterone's role to promote various pathogenic pathways that result in HFrEF and CKD. These mechanisms include modulating the effect of angiotensin II on plasminogen activator inhibitor-1 expression, stimulating transforming growth factor β 1 synthesis, generating reactive oxygen species, promoting glomerular, and podocyte remodeling and albuminuria. The clinical implications of the interplay of finerenone and the components of the renin-angiotensin cascade (angiotensinogen, Ang-[1–12], Ang II, and Ang-[1–7]) are of great interest.

By way of introduction, a robust literature now documents that dysfunction in the balance between the ACE/Ang II/AT1-R and ACE2/Ang-(1–7)/Mas-R axes contributes to the pathogenesis of essential hypertension, adverse cardiac and vascular remodeling, diabetes mellitus,

and CKD [46]. The potential influence of the ACE2/Ang-(1–7)/Mas-R axis in the control of aldosterone secretion and renal modulation of its activity remains poorly studied. While Ang-(1–7) has no direct agonistic activity on aldosterone secretion, the heptapeptide has been reported to act as a negative modulator of aldosterone secretion in vitro and in vivo [47]. Of significant interest are studies showing that spironolactone can reverse the inhibitory action of aldosterone on ACE2 gene expression and activity [47–51]. If confirmed, these early studies may be of critical importance as ACE2 is the enzyme accounting for the ineffectiveness of the coronavirus SARS-CoV-1 and SARS-CoV-2 [52–54].

Combination Therapy with an SGLT-2i Inhibitor and an MRA

The comprehensive management of DKD depends in great part on combination treatment regimens targeting the wide array of complications of T2DM. Combination therapy with an SGLT-2i and an MRA has recently been advocated as the “next step” for treating HFREF and CKD progression. To provide context, the potential advantages of fixed-dose combination medications have been reviewed extensively [55]. SGLT-2is and MRAs may have complementary mechanisms of action and may constitute an attractive combination for the treatment of both HFREF and CKD. Recent preclinical studies by Kolkhof et al. [56] in a nondiabetic cardiorenal rat model have demonstrated that treatment with the combination of the novel nonsteroidal MRA finerenone and the SGLT-2i empagliflozin conferred renal protection, as assessed by an efficacious reduction in proteinuria, renal lesions, and mortality. These findings support a potential for combined clinical use in cardiorenal patient cohorts [57]. A recent paper by Vaduganathan et al. [58] aggregated data from 3 previously reported randomized controlled trials to estimate lifetime gains in event-free survival and overall survival with comprehensive therapy versus conventional therapy in patients with chronic HFREF. They concluded that the anticipated aggregate treatment benefits of early comprehensive disease-modifying pharmacological therapy are substantial and support the combined use of an ARNI, β blocker, MRA, and SGLT-2i. This analysis is consistent with the formulation that combination therapy with 2 drugs, an SGLT-2i and a nonsteroidal MRA, may confer complementary benefits exceeding the benefits of either class alone. The newly registered MIRACLE (Efficacy, Safety, and Tolerability of AZD9977 and Dapagliflozin in Participants With Heart Failure and CKD) trial will investigate potential benefits of combining

SGLT-2i and MRA treatment in patients with HFREF and CKD (NCT04595370) [59].

The Interrelationship of FGF23 and Aldosterone May Be a Propitious Subject for Future Investigation

Plasma levels of fibroblast growth factor (FGF23) are elevated in cardiac and renal failure and are associated with poor clinical prognosis of both disorders [60]. The RAAS upregulates various tubular sodium cotransporters that are also targets of FGF23 and its co-receptor Klotho [60, 61]. Excessive FGF23 levels and hyperaldosteronism are further observed in Klotho-deficient mice. Consequently, it would be of interest to conduct studies to further elucidate the interrelationship of FGF23 and aldosterone and the response to an intervention of treatment with a nonsteroidal MRA. A caveat is in order. In interpreting these experimental findings and ostensible differences in these proposed studies, it must be borne in mind that there are many variables to consider, including differences in animal models, strains, degree of hypertension, and when the intervention was initiated.

Conclusion

Recent studies have demonstrated a wider and expanded role for aldosterone in nonepithelial activity, thereby influencing inflammation, collagen formation, fibrosis, and necrosis. Increasing evidence has accrued that clearly implicates the pathophysiological overactivation of the MR as a major determinant of progression of CKD and its associated morbidity and mortality. In accord with this formulation, MR antagonism is currently being investigated as a novel treatment regimen to retard the progression of CKD. The recently reported FIDELIO-DKD study demonstrated that patients with CKD and T2D who were treated with finerenone (a novel nonsteroidal MRA) manifested a lower risk of a primary outcome event (kidney failure, a sustained decrease of $\geq 40\%$ in the estimated glomerular filtration rate from baseline, or death from renal causes) than patients in the comparator arm who received placebo. Based on the success of the FIDELIO-DKD study, future studies should be implemented testing the hypothesis that a wide array of nondiabetic CKD clinical cohorts, many of which are underserved, are also modulated by overactivation of the MR. Consequently, these nondiabetic CKD cohorts may be amenable to treatment with novel nonsteroidal MRAs.

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