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The mineralocorticoid receptor in chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a major public health concern, affecting approximately 10% of the population worldwide. CKD of glomerular or tubular origin leads to the activation of stress mechanisms, including the renin angiotensin aldosterone system and mineralocorticoid receptor (MR) activation. Over the last two decades, blockade of the MR has arisen as a potential therapeutic approach against various forms of kidney disease. In this review, we summarize the experimental studies that have shown a protective effect of MR antagonists (MRAs) in non-diabetic and diabetic CKD animal models. Moreover, we review the main clinical trials that have shown the clinical application of MRAs to reduce albuminuria and, importantly, to slow CKD progression. Recent evidence from the FIDELIO trial showed that the MRA finerenone can reduce hard kidney outcomes when added to the standard of care in CKD associated with type 2 diabetes. Finally, we discuss the effects of MRAs relative to those of SGLT2 inhibitors, as well as the potential benefit of combination therapy to maximize organ protection.

Non-standard abbreviations:

CKD: Chronic kidney disease

GFR: Glomerular filtration rate

MR: Mineralocorticoid receptor

RAAS: Renin angiotensin aldosterone system

ACE: Angiotensin converting enzyme

MRAs: Mineralocorticoid receptor antagonists

ROS: Reactive oxygen species

NADPH: Nicotinamide adenine dinucleotide phosphate

TGF- β : Transforming growth factor- β

MCP-1: Monocyte chemoattractant protein-1

NOS: Nitric oxide synthase

UUO: Unilateral ureteral obstruction

PKD: Polycystic kidney disease

AKI: Acute kidney injury

RCT: Randomized controlled trials

T2D: Type 2 diabetes

UACR: Urine albumin-to-creatinine ratio

ARB: Angiotensin II receptor blocker

SGLT: Sodium-glucose transporter

1- Functions of the kidney, definitions of kidney injury, and staging of kidney diseases

The kidney is the key organ that maintains body homeostasis, i.e., the balance of water, salt, acids and bases, potassium, bone minerals, metabolic waste excretion, and oxygen sensing to regulate red blood cell production (Table 1). The filtration barrier of the kidney is fundamental for these processes and, hence, maintaining this barrier is another important function of the kidney. Although urine is no more than a side product of the aforementioned kidney functions, conceptually similar to air pollution not being a function but a side product of a technical plant, urinary abnormalities frequently indicate kidney dysfunction.

Chronic kidney disease (CKD) is defined by structural and functional abnormalities of the kidneys lasting more than three months, whereas “functional abnormalities” can also refer to impaired barrier function (albuminuria) or tubular function (electrolyte abnormalities) of the kidneys ("Chapter 1: Definition and classification of CKD," 2013). Instead, stages of CKD refer exclusively to clearance of the intrinsic metabolite creatinine (converted with formulas into an estimated glomerular filtration rate (GFR)) and to albuminuria as a marker of filtration barrier integrity.

2- Overview of the pathophysiology of chronic kidney disease

2.1 Glomerular disorders

Persistently impaired kidney function can have many causes, involving a large spectrum of diverse pathophysiological mechanisms. Regardless of when the injurious process in the glomerular compartment starts, e.g., in genetic podocytopathies or glomerulonephritis, proteinuria is an early sign of filtration barrier injury and dysfunction (Kopp et al., 2020). Persistent proteinuria is frequently a sign of podocyte injury, which frequently progresses to irreversible glomerulosclerosis and nephron loss. Proteinuria increases the metabolic workload and cellular stress for the respective proximal tubule as it attempts to minimize the urinary loss of protein by maximizing protein breakdown in the brush border and transcellular reabsorption, which is energy consuming (Sharma & Smyth, 2021). As the cellular stress in both compartments continues, irreversible loss of epithelial cells from glomeruli and tubules ultimately leads to the loss of entire nephrons. As the

number of functioning nephrons declines, the filtration and reabsorption load for the remaining nephrons increases. A typical sign of single nephron hyperfiltration is an increase in proteinuria, which perpetuates the stress for the respective tubules (Anders, Huber, Isermann, & Schiffer, 2018). Structural adaptations include cell hypertrophy and nephromegaly, which further drive glomerular scarring and interstitial fibrosis, both structural hallmarks of nephronopenia, requiring structural adaptations (Helal, Fick-Brosnahan, Reed-Gitomer, & Schrier, 2012; Hostetter, Olson, Rennke, Venkatachalam, & Brenner, 1981). The traditional concept that interstitial fibrosis itself contributes to nephron loss and CKD progression in glomerular disorders is poorly supported by the data (Kalluri & Neilson, 2003). It is, therefore, of no surprise that drugs with specific antifibrotic effects fail to prevent CKD progression, (Voelker et al., 2017), whereas drugs that reduce the hemodynamic and metabolic nephron overload of nephrons strongly attenuate CKD progression (Heerspink et al., 2020).

2.2 Tubular disorders

CKD can arise from disorders that primarily affect the tubules, e.g., CKD following an episode of acute tubular necrosis, cystic kidney diseases, nephrocalcinosis, interstitial nephritis, IgG4 disease, and others (Romagnani et al., 2017). Such tubular injuries involve interstitial inflammation and fibrosis early on, even before nephron loss. Irreversible tubule injury leads to tubule atrophy and corresponding non-functional atubular glomeruli. (Chevalier & Forbes, 2008). In addition, nephron loss results in an overload of the remaining nephrons, i.e., secondary filtration stress to the glomerular compartment and additional metabolic stress to the remaining tubules, driving further tubule cell loss and interstitial inflammation and fibrosis.

2.3 Adaptation to nephron injury involves stress response programs

Tissue injury triggers response programs that have been positively selected by evolution to increase survival, such as the coagulation cascade, inflammation, epithelial hypertrophy, stem-cell proliferation, and scarring (Anders, 2012). Each of these programs comes at the cost of trade-offs, such as immunopathology, cancer, and organ fibrosis, which all drive chronic organ dysfunction in those that survive the injury phase (Lei & Anders,

2017). Several signaling pathways play a key role in the stress response, including activation of the renin-angiotensin-aldosterone system (RAAS) and the neurohumoral axis, both leading to activation of the [mineralocorticoid receptor](#) (MR). They are both activated locally inside the kidney and systemically. Therefore, blocking these systems can minimize such trade-offs and improve outcomes in chronic organ failure. For example, beta-receptor blockers, [angiotensin converting enzyme](#) (ACE) inhibitors, and [angiotensin receptor](#) blockers (ARBs) improve outcomes of heart failure (van der Horst, Voors, & van Veldhuisen, 2007). In addition, ACE inhibitors and ARBs also improve CKD (Ruggenenti et al., 1999; Vaduganathan et al., 2020). Similarly, MR agonists (MRAs) improve the outcomes of heart failure and CKD (Capelli et al., 2020), the latter discussed in more detail in this review.

An overview of the glomerular and tubulointerstitial causes of CKD is presented in Figure 1, along with the therapeutic approaches to slow CKD progression during the advancing stages of CKD by directly targeting the kidney or providing the control of cardiovascular risk.

3- The MR and chronic kidney disease without diabetes

Several studies have shown that MR activation can occur outside of aldosterone-sensitive distal nephrons, including in vascular cells, inflammatory cells, podocytes, mesangial cells, and fibroblasts. The pathophysiological consequences of MR activation in these cells includes increased ROS generation, macrophage polarization towards an inflammatory state, T-cell activation, increased production of extracellular matrix proteins, leading to fibrotic remodeling, and hemodynamic alterations (for a review see (Barrera-Chimal, Girerd, & Jaisser, 2019)). Therefore, antagonizing the MR is an attractive therapeutic strategy to limit kidney injury by blocking these pathological mechanisms. In addition, nongenomic effects of aldosterone, including ROS generation by NADPH oxidase, hemodynamic effects and signaling by ERK1/2 and c-Jun, increased intracellular calcium, and protein kinase C activation have been reported (for a review see (Mihailidou, Tzakos, & Ashton, 2019)). Thus, the benefit of MRAs may also be mediated by blocking the nongenomic effects of aldosterone. For example, MRAs reduce hyperfiltration by the prevention of aldosterone-induced preferential vasoconstriction of efferent versus afferent

renal arterioles (Arima et al., 2003), most likely explaining the rapid antiproteinuric effects of MRAs (G. L. Bakris et al., 2020; Bianchi, Bigazzi, & Campese, 2005).

Over the last decade, extensive research has led to the development of fourth-generation nonsteroidal MRAs (Kolkhof, Nowack, & Eitner, 2015). The pharmacological differences between steroidal and non-steroidal MRAs are extensively reviewed elsewhere (Agarwal et al., 2021). Briefly, physicochemical and tissue penetration characteristics between these compounds may differ, leading to differential tissue distribution. For example, the nonsteroidal MRA finerenone shows balanced distribution between the heart and kidneys versus spironolactone or eplerenone, which preferentially concentrate in the kidneys (Kolkhof et al., 2014). Another difference is that finerenone has a shorter half-life than steroidal MRAs and does not have active metabolites, thus potentially reducing its long-term effects on sodium/potassium balance (Agarwal et al., 2021). Furthermore, nonsteroidal MRAs differ from steroidal MRAs in co-factor recruitment after binding to the MR, which may result in differential modulation of gene expression, leading to a stronger inhibition of inflammation and fibrosis at equi-natriuretic doses (Grune et al., 2018).

3.1 MR antagonism alleviates kidney injury in various pre-clinical models of kidney disease without diabetes

Kidney fibrosis is the common result of CKD of various origins. Pioneering studies demonstrated that spironolactone treatment of rats with subtotal nephrectomy transiently reduces proteinuria, lowers blood pressure, and reduces cardiac hypertrophy (Greene, Kren, & Hostetter, 1996). It was later found that spironolactone treatment can also induce the regression of glomerulosclerosis in this subtotal nephrectomy CKD model (Aldigier, Kanjanbuch, Ma, Brown, & Fogo, 2005). Recently, the non-steroidal aldosterone antagonist Ly was also shown to protect against albuminuria and kidney hypertrophy in the remnant kidney model with better efficacy than eplerenone (Fujihara et al., 2017).

MR inhibition has also shown protective effects in animal models of glomerulonephritis. In mice with proliferative glomerulonephritis induced by anti-Thy1.1 antibody, spironolactone showed antiproteinuric effects and reduced TGF- β levels and glomerular injury and proliferation (Asai et al., 2004) (Gullulu, Akdag, Kahvecioglu, Filiz, & Savci, 2006). In this model, eplerenone administration also has anti-inflammatory effects,

as shown by decreased glomerular macrophage infiltration, MCP-1 expression, and mesangial phenotypic activation (Qin et al., 2013). Eplerenone also reduced albuminuria, glomerular sclerosis, and crescents in glomerulonephritis induced by anti-glomerular basement membrane antibody administration, accompanied by reduced infiltration of CD4⁺ and CD8⁺ T cells and macrophages (Zitt et al., 2011) (Huang et al., 2014). The non-steroidal MRA BR-4628 also helped to maintain renal function, prevented glomerular tuft damage, and reduced glomerular crescents by 50%, accompanied by reduced macrophage and T-cell infiltration (Ma, Han, Nikolic-Paterson, Kolkhof, & Tesch, 2015).

MR antagonism has shown beneficial effects in several models of hypertension-induced kidney injury that are independent from the effect on lowering blood pressure. Spironolactone prevented the appearance of nephrosclerotic injury and proteinuria in stroke-prone spontaneously hypertensive rats (SHRs), even in the absence of blood pressure control (Rocha, Chander, Zuckerman, & Stier, 1999). The new non-steroidal MR antagonist KBP-5074 demonstrated better efficacy than eplerenone in reducing blood pressure, albuminuria, and kidney hypertrophy and injury in Dahl salt-sensitive rats and stroke-prone SHR (Cp, 2017). In SHR, in which chronic NOS inhibition exacerbates kidney lesions, eplerenone administration reduced proteinuria and structural lesions, despite there being no modifications in systemic or renal hemodynamics (Zhou, Ono, Ono, & Frohlich, 2004). Similarly, glomerular sclerosis and proteinuria were prevented in a radiation injury hypertensive model (Brown et al., 2000). Eplerenone prevented podocyte injury and effacement, with a consequent delay in proteinuria and glomerulosclerosis, in the Dahl salt hypertensive rat model (Nagase et al., 2006). Thus, MR inhibition could help to maintain the glomerular filtration barrier through preventing podocyte damage. In Dahl rats, the non-steroidal MRA esaxerenone reduced blood pressure, albuminuria, and structural injury (Li et al., 2019). In transgenic hypertensive rats (Cyp11a1Ren2 rats), spironolactone treatment started after the establishment of hypertension reduced proteinuria and halted glomerulosclerosis and the progression of fibrosis, independently of blood pressure normalization (Leader, Kelly, Sammut, Wilkins, & Walker, 2020).

In mineralocorticoid-induced hypertension, eplerenone reduced hypertension and blunted albuminuria, kidney injury, and pro-inflammatory gene expression in Sprague-Dawley rats with aldosterone-salt plus unilateral nephrectomy (Blasi et al., 2003). The non-

steroidal MRAs SM-368229, CS-3150 (esaxerenone), and AZD9977, have also shown promising effects on renal pathology in this context (Nariai et al., 2012) (Bamberg et al., 2018) (Arai, Morikawa, Ubukata, Tsuruoka, & Homma, 2016). Similarly, the non-steroidal MRA KBP-5074 showed a better therapeutic index than eplerenone in a rat model of kidney injury induced by aldosterone, salt, and unilateral nephrectomy (Jaisser et al., 2021). Of note, AZ9977 showed a reduced effect on renal sodium excretion relative to that of eplerenone, while retaining its renal protection benefit (Bamberg et al., 2018).

A widely used model of kidney fibrosis consists of unilateral ureteral obstruction (UUO). Spironolactone reduced kidney fibrosis in mice subjected to UUO for two weeks (Trachtman, Weiser, Valderrama, Morgado, & Palmer, 2004). In rats with UUO, eplerenone inhibited renal fibrosis and inflammation and reduced monocyte and macrophage infiltration, interstitial cell proliferation, and oxidative stress (Chen et al., 2013). Moreover, it also attenuated the fibrosis that develops in the contralateral kidney of UUO rats via inhibition of the macrophage to myofibroblast transition. (Xiong et al., 2021)

In a rat model of polycystic kidney disease (PKD), spironolactone treatment attenuated hypertension in female rats only. Spironolactone reduced albuminuria and plasma creatinine, but fibrosis and cyst size were not modified. Thus, MR antagonism was only partially protective against kidney injury in the rat PKD model (Jeewandara et al., 2015).

In kidney injury due to ischemia, spironolactone administration, before or even up to three hours after bilateral renal IR injury in the rat, limited acute kidney dysfunction and tubular injury by preventing the sustained fall in renal blood flow, reducing oxidative injury, increasing endothelial nitric oxide synthase activation, and inducing metabolic reprogramming (Mejia-Vilet et al., 2007) (Sanchez-Pozos et al., 2012) (Lindhardt et al., 2020). MR antagonism with the non-steroidal MRAs BR-4628 and finerenone showed similar protective effects in rat and mouse models of ischemic acute kidney injury (AKI) (Barrera-Chimal et al., 2016) (Lattenist et al., 2017). MR antagonism in ischemic AKI was further shown to be protective in the white large pig AKI pre-clinical model, in which MR antagonism with potassium canrenoate reduced urinary tubular injury markers and oxidative stress levels and, importantly, preserved kidney function and structure (Barrera-Chimal et al., 2017) (Melis et al., 2019). Moreover, spironolactone and finerenone have also been shown to be effective in preventing the transition to CKD following an ischemic AKI episode

in rats and mice (Barrera-Chimal et al., 2013) (Barrera-Chimal et al., 2015) (Barrera-Chimal et al., 2018; Lattenist et al., 2017). Importantly, potassium canrenoate administration in the white large pig AKI model was also able to prevent AKI-induced CKD progression, with reduced kidney fibrosis and improved kidney function 90 days after the AKI episode (Barrera-Chimal et al., 2018). Thus, pre-clinical evidence supports MR antagonism as a reasonable strategy to prevent the acute and chronic alterations induced by ischemic AKI, which should be further explored in dedicated clinical trials.

In the transplantation setting, a chronic allograft dysfunction model in dark agouti to Wistar Furth rat kidney transplantation, spironolactone treatment from two days before and up to 12 weeks after transplantation significantly reduced vasculopathy and glomerular macrophage influx and showed a trend towards reduced proteinuria and glomerulosclerosis (Waanders et al., 2009). However, neither MR antagonism nor the inhibition of aldosterone synthase showed any protection against glomerulosclerosis or interstitial fibrosis in male Fisher-344 to male Lewis rat allograft injury (Lahmer et al., 2012). The use of calcineurin inhibitors as immunosuppressive drugs in organ transplantation is frequently restricted due to their acute or chronic nephrotoxic consequences. Spironolactone treatment of rats with acute cyclosporine A (CsA) nephrotoxicity was shown to maintain kidney function (McAuley, Whiting, Thomson, & Simpson, 1987) and prevent the reduction in renal blood flow (J. M. Perez-Rojas et al., 2005). Eplerenone displayed a similar protective effect (Nielsen, Jensen, Marcussen, Skott, & Bie, 2008). MR deletion in smooth muscle cells prevents the acute kidney dysfunction and injury induced by CsA (Amador et al., 2016). Spironolactone also prevented the fall in renal blood flow and GFR and prevented/or treated the tubulointerstitial fibrosis/expansion and arteriopathy observed in a rat model of chronic calcineurin nephrotoxicity (J. M. Perez-Rojas et al., 2005) (Feria et al., 2003) (J. Perez-Rojas et al., 2007) (Nielsen, Jensen, Hansen, Marcussen, & Bie, 2013).

As summarized in Figure 2, MRAs have shown beneficial effects in several preclinical models of kidney disease associated with hypertension, glomerulonephritis, and calcineurin inhibitor use and in fibrotic kidney disease and kidney transplantation settings. Non-steroidal MR antagonists show similar or even enhanced beneficial effects in pre-clinical models of kidney disease, thus supporting their clinical use for this indication.

3.2 Clinical trials on mineralocorticoid receptor antagonism in kidney diseases without diabetes

Evidence for the effectiveness of MR antagonism in hard kidney disease outcomes is limited due to concerns about hyperkalemia in patients with reduced renal function. Clinical trials have thus far been limited due to the restricted use of MRAs in patients with advanced CKD.

Several randomized controlled trials (RCTs) have focused on the antiproteinuric effect of MRAs in CKD patients. Meta-analyses of these studies (Bolignano, Palmer, Navaneethan, & Strippoli, 2014) (Currie et al., 2016) (Alexandrou et al., 2019) (Chung et al., 2020) showed that MRAs have a potent effect in reducing proteinuria, the urine albumin-to-creatinine ratio (UACR), and albumin excretion, alone or when they are combined with ACE inhibitors and ARBs. An antiproteinuric effect of MRAs has been reported in glomerulonephritis (Yu et al., 2018).

In non-diabetic CKD, a recent single-blinded placebo-controlled trial that randomized 48 patients with stage 2-3 CKD and plasma aldosterone > 15 ng/dL to eplerenone (25 mg/d) or placebo found that the estimated GFR (eGFR) dropped in the first six months after the initiation of eplerenone. However, at months 24 and 36, the eGFR was maintained and significantly higher than in the placebo arm (Minakuchi et al., 2020). In a retrospective analysis of pre-dialysis patients with stage 3-4 CKD, it was found that spironolactone users (n = 693) had a 34% lower risk of end-stage renal disease progression than non-users (n = 1,386), but hyperkalemia-associated hospitalization rates were also higher (Yang, Kor, & Hsieh, 2018). The phase 2b BLOCK-CKD trial evaluated the efficacy and safety of the non-steroidal MRA KBP-5074 (0.25 and 0.5 mg/day) versus a placebo in 162 patients with stage 3b/4 CKD and resistant hypertension (G. Bakris, Yang, & Pitt, 2020) (G. Bakris et al., 2021). After 84 days of follow-up, KBP-5074 significantly reduced systolic blood pressure by 7 mmHg in the 0.25 mg/day and 10.2 mmHg in the 0.5 mg/day groups. The incidence of hyperkalemia was similar among the placebo and KBP-5074 groups, with no hyperkalemia events above 6.0 mmol/L observed and no hyperkalemia-related hospitalizations recorded (G. Bakris et al., 2021).

MR antagonism was tested in a pilot trial on 20 living-donor kidney transplantation (KT) patients, in which spironolactone (25 mg) was administered from one day before up to

three days after KT and resulted in a reduction in oxidative stress markers in the urine (Ojeda-Cervantes et al., 2013). This effect was later confirmed in another study, in which higher spironolactone doses (50 and 100 mg, n = 25) reduced urinary 8-hydroxylated-guanosine levels, as a marker of oxidative stress, relative to a placebo in living-donor KT patients (n = 27) (Morales-Buenrostro et al., 2019). As these studies were performed on a small number of patients, more highly powered studies to evaluate the effect in postmortal donor KT, with a longer follow-up, are expected and will yield more information about the efficacy of MR antagonism in preventing delayed graft function and chronic effects. Indeed, the multicenter RCT EPURE, to evaluate the impact of short-term administration of eplerenone (immediately before and four days after KT) on three-month renal graft function in patients receiving a graft from an expanded-criteria donor, is currently ongoing and expected to randomize 132 patients (NCT02490904) (Girerd et al., 2018).

Concerning calcineurin toxicity in transplant patients, one RCT showed promising results, indicating that eplerenone may be helpful in reducing biopsy-proven chronic graft nephropathy in 23 pediatric patients (Medeiros et al., 2017). The SPIREN trial (NCT01602861) is currently evaluating the efficacy of spironolactone administration for three years among 170 prevalent kidney transplant patients. The primary endpoint is GFR, measured by chrome-EDTA clearance. Secondary outcomes are proteinuria, the amount of interstitial fibrosis in graft biopsies, and cardiovascular events (Mortensen et al., 2018). Of note, it was reported that spironolactone treatment for one year was not associated with changes in markers of endothelial dysfunction in a subgroup analysis of 80 patients from this trial (Mortensen et al., 2019).

Further studies are warranted in this area. It would be of interest to evaluate non-steroidal MRAs in chronic allograft dysfunction, in which chronic MRA use is currently prohibited. Moreover, the impact of MRAs on the CV comorbidities associated with KT should be assessed based on the CV benefit reported in other settings.

Spironolactone administration in 115 cardiac surgery patients, 100 mg the day before surgery and 25 mg/d during the three days after the procedure, did not demonstrate a benefit in post-operative AKI relative to placebo (n = 118) (Barba-Navarro et al., 2017). Indeed, a trend towards an increased risk in the spironolactone arm was observed (Barba-Navarro et al., 2017). Nonetheless, the trial was underpowered due to not achieving the planned sample

size and randomization led to a higher proportion of diabetic patients in the spironolactone group (31 vs 18%, $p = 0.02$). In a RCT in which the primary outcome was to test whether RAAS inhibition reduced the prevalence of atrial fibrillation after cardiac surgery, spironolactone was protective against AKI but no benefit was observed for atrial fibrillation (Pretorius et al., 2012). Ongoing trials will evaluate whether spironolactone can reduce the incidence and severity of AKI in critically ill patients on invasive mechanical ventilation when administered during the first five days of critical care after admission to the unit (NCT03206658) and the effect of short-term spironolactone administration on AKI prevention in postoperative patients following major surgery (NCT02531412). An additional study will evaluate spironolactone (200 mg/single dose) or placebo in contrast-induced nephropathy (NCT03329443) (Mujtaba et al., 2018).

In conclusion, the use of MRAs in pre-clinical models shows promise in targeting the development of fibrosis in the kidney due to various etiologies. Although the evidence in humans is scarce, post-hoc analyses of the effect of MRAs in cardiovascular-focused trials in which patients with reduced renal function were included, together with proof-of-concept trials, demonstrate that MR antagonism has beneficial effects on kidney health, despite the risk of hyperkalemia (Figure 2).

4. MR and kidney disease with diabetes / metabolic disease

4.1 The role of diabetes in CKD

Hyperglycemia induces immediate single nephron hyperfiltration via the deactivation of tubulo-glomerular feedback following a fascinating series of events, explained in detail elsewhere. Almost all young patients with type 1 diabetes and good nephron function easily handle diabetes-related hyperfiltration of the kidney and do not develop kidney damage for many decades, if at all. Indeed, this form of diabetic nephropathy has become rare for those with access to insulin (pump) therapy.

The onset of hyperglycemia in older people usually adds to precedent nephronopenia due to kidney ageing, previous injury, or concomitant nephropathies. In addition, type 2 diabetes (T2D) usually involves obesity, which is an independent cause of kidney overload. As such, it is no surprise that adults with T2D develop macroproteinuria at higher rates and

much faster than young individuals without such comorbidities. Therefore, the concept of “diabetic kidney disease (DKD)” in adults is outdated and is now referred to as “CKD with diabetes”. Indeed, in adults, the hemodynamic and metabolic stress imposed by diabetes on adult kidneys acts mostly as a cofactor to accelerate the progression of CKD, which at this age is generally of multifactorial nature.

4.2 MR antagonism alleviates kidney injury in various pre-clinical models of kidney disease associated with diabetes or metabolic disease

Several studies performed in mouse and rat models of type 1 or type 2 diabetes have shown that steroidal MRAs are effective in preventing kidney alterations, including excessive extracellular matrix deposition in the glomeruli and interstitium, oxidative injury, inflammatory cell infiltration, and proteinuria (Fujisawa et al., 2004; Guo et al., 2006; K. H. Han et al., 2006; S. Y. Han et al., 2006; Yuan, Jia, & Bao, 2007). MRA use in DKD also prevents podocyte injury by reducing oxidative stress and activating autophagy (Dong et al., 2019; Toyonaga et al., 2011). As diabetes and hypertension often co-exist, the effect of spironolactone and eplerenone in mouse models of hypertensive and diabetic injury has also been explored, showing that both MRAs reduce albuminuria and fibrosis (Lian et al., 2012; Pessoa, Peixoto, Papadimitriou, Lopes de Faria, & Lopes de Faria, 2012).

More recently, the efficacy of non-steroidal MRAs in diabetic models of kidney disease has been explored. Esaxerenone demonstrated protection against glomerular lesions, fibrosis, inflammation, and albuminuria in hypertensive mice with T2D (Bhuiyan et al., 2019). Of note, these beneficial effects were more pronounced for esaxerenone than for spironolactone, whereas the blood pressure was reduced to a similar extent (Bhuiyan et al., 2019). The nonsteroidal MRA AZD9977 was shown to reduce glomerular extracellular matrix deposition in type 2 diabetic db/db mice (Bamberg et al., 2018).

Obesity and metabolic co-morbidities often lead to kidney injury. In a severe model that combines obesity, hypertension, and high salt (SHR/cps rat), massive proteinuria, severe renal lesions, and podocyte injury are observed. Eplerenone dramatically improved the proteinuria and renal injury of these animals (Nagase, Matsui, Shibata, Gotoda, & Fujita, 2007). Mice with obesity induced by a high-fat diet develop kidney injury, characterized by glomerular hypercellularity, mesangium expansion, albuminuria, and increased rho kinase

activity; all these alterations were attenuated by eplerenone (Tokuyama et al., 2012). High glucose increases Rac1 and MR transcriptional activity in cultured mesangial cells (Yoshida et al., 2014). In accordance with these observations, the inhibition of Rac1 reduced MR activity in the kidney and mitigated renal pathology in a mouse model of obesity-related T2D (KKA(y) mouse), even if plasma aldosterone levels were unchanged. (Yoshida et al., 2014) The non-steroidal MR antagonist finerenone improved metabolic syndrome-related nephropathy in rats with metabolic syndrome (Zucker fa/fa rats) by reducing proteinuria and neutrophil gelatinase-associated lipocalin (NGAL) levels(Lachaux et al., 2018).

4.3 Clinical trials on mineralocorticoid receptor antagonism in kidney diseases with diabetes

One meta-analysis of 16 studies including 789 DKD patients showed that spironolactone plus an ACE inhibitor or ARB significantly diminishes 24-h urinary albumin/protein excretion or the urinary albumin/creatinine ratio (Hou, Xiong, Cao, Wen, & Li, 2015). As blood pressure was also reduced, it is possible that the antiproteinuric effect may be, at least partially, mediated by the reduction of blood pressure.

High dose eplerenone administered to 70 T2D patients with a high risk of cardiovascular disease had a remarkable effect on UACR reduction versus a placebo (n = 70), while maintaining an acceptable safety level (Brandt-Jacobsen et al., 2020). The non-steroidal MRA finerenone was first tested in DKD patients to evaluate its safety and efficacy for renal outcomes in the ARTS-DN study, in which a dose-dependent reduction of proteinuria was observed with finerenone in DKD patients receiving ACE inhibitors or ARBs (G. L. Bakris et al., 2015). These data led to the FIDELIO RCT, in which 5,734 patients with CKD and T2D were randomized to receive finerenone or placebo to evaluate the effects of finerenone on renal outcomes. After a 2.6-year median follow-up, finerenone was shown to reduce the primary renal outcome (a composite of time-to event, kidney failure, sustained decrease of at least 40% of baseline eGFR, or death from renal causes) by 18% (G. L. Bakris et al., 2020). A secondary outcome of a sustained decrease of > 57% in eGFR from baseline was reduced by 32% in the finerenone arm. The adverse events were similar for the placebo and finerenone groups, whereas hyperkalemia was more common in the finerenone (2.3%) than placebo (0.9%) group (G. L. Bakris et al., 2020). Other non-steroidal MR antagonists have also shown promising results in DKD. The non-steroidal MRA aprepironone showed a

significant reduction in UACR when administered for 24 weeks to stage 2 DKD patients (Wada et al., 2020). Similar anti-albuminuric effects were observed with esaxerenone treatment combined with RAS inhibitors for 12 weeks in patients with T2D and microalbuminuria (Ito, Shikata, Nangaku, Okuda, & Sawanobori, 2019). Therefore, MR antagonism is a useful strategy to reduce hard renal outcomes in DKD patients.

In conclusion, Phase-2 clinical trials in DKD have been concluded for non-steroidal MR antagonists, such as esaxerenone and apararenone, while the largest phase-3 clinical trial in DKD patients has been concluded for finerenone, with very exciting data on the prevention of hard renal outcomes.

5- Sodium-glucose transporter inhibitors versus MR antagnoism

The journey of basic and clinical MR research has been exciting because the dual effects of MRAs on the kidney itself and on the related cardiovascular comorbidity address many of the unmet medical needs of CKD patients, with or without diabetes (Agarwal et al., 2021; Barrera-Chimal et al., 2019). However, the evolving pathophysiological concept of hemodynamic and metabolic overload of a declining number of nephrons leaves space for numerous other molecular targets with potential renoprotective effects (Romagnani et al., 2017). Among them, inhibitors of the [sodium-glucose transporter \(SGLT\)-2](#) are particularly potent. SGLT2 is expressed in the S2 and S3 segment of the proximal tubule, where it recovers sodium and glucose from the glomerular filtrate and therefore minimizes glucose loss into the urine (Vallon, 2015). The development of SGLT2 inhibitors as anti-diabetic drugs was based on the rationale of enhancing urinary glucose excretion and, indeed, SGLT2 inhibitors can reduce Hba1c by up to 1% and the negative calorie balance is associated with a reduction in lean body weight (Scheen, 2020). However, SGLT2 inhibition revealed an unexpected potency to reduce cardiovascular events by approximately 30 to 40% and several markers of CKD progression by 40 to 60% in large clinical trials that included patients with T2D, heart failure, and/or CKD (Perkovic et al., 2019; Wanner et al., 2016; Zannad et al., 2020; Zinman et al., 2015). Of note, background treatment with RAS inhibitors was 90% or more in all these trials (Perkovic et al., 2019; Wanner et al., 2016; Zannad et al., 2020; Zinman et al., 2015). A debate about the underlying mechanisms-of-action is still ongoing and includes diverse concepts, which are discussed elsewhere in detail (Thomas & Cherney,

2018; Vallon, 2015). Briefly, SGLT2 inhibition reduces the increased workload of the remaining nephrons of CKD kidneys in two ways. First, SGLT2 inhibition directly attenuates the workload of the proximal tubules by blocking sodium and glucose reuptake, which increases in the remaining nephrons as other nephrons undergo atrophy for reasons of aging or injury. (Vallon, 2015) Second, SGLT2 inhibition indirectly reduces the abnormal and cumbersome hyperfiltration of the remaining nephrons, i.e., mechanical shear stress at the delicate glomerular filtration barrier, and therefore reduces barrier injury, proteinuria, and glomerulosclerosis (Anders, Davis, & Thurau, 2016; Thomas & Cherney, 2018). Less glomerular filtration also implies less workload to the respective proximal tubules. Conceptually similar to beta-blockers, which reduce the workload of failing hearts, SGLT2 inhibitors reduce the workload of failing kidneys, which translates into longer organ survival.

The average effect size of a RAS/SGLT2 inhibitor combination exceeds the effect size of a RAS/finerone combination for primary kidney endpoints in patients with T2D and CKD, as reported by the FIDELIO trial (G. L. Bakris et al., 2020; Perkovic et al., 2019; Wanner et al., 2016). At this point, it is uncertain whether this difference will repeat in other patient cohorts, e.g., in patients with non-diabetic kidney disease or heart failure. Given the different mechanisms-of-actions of SGLT2 inhibition and MR antagonism, one may speculate that a triple combination may be even more potent than either of the dual combinations. In support of an additive effect of SGLT2 inhibitors and MRAs, it was recently shown that a low-dose combination of finerenone and empagliflozin showed an additive effect in the reduction of albuminuria and cardiorenal structural lesions in hypertensive rats relative to monotherapies (Kolkhof et al., 2021). In particular, the diuretic effect of SGLT2 inhibitors could minimize the risk of MRA-related hyperkalemia, one of the remaining safety concerns for broad implementation of MRAs (Agarwal et al., 2021; Vukadinovic et al., 2017). The FIDELIO trial included only 5% of patients on SGLT2 inhibitors in the MRA arm (G. L. Bakris et al., 2020), which does not yet allow any conclusion to be drawn on this timely question. However, the prospect of more potent combination therapies is tempting in light of additive renoprotective effects, as well as related cardiovascular morbidity.

Summary

The role of MR signaling as an acute stress-response mechanism that can remain activated and promote chronic organ injury renders the MR a therapeutic target for many chronic disorders. Experimental and clinical MR research has come a long way and has consistently demonstrated the protective effects of MRAs on failing kidneys and the associated cardiovascular disease. There are still several safety concerns, even with new generation MRAs, e.g., hyperkalemia, which, however, is susceptible to co-administration of diuretics. Given the potent renoprotective effects of SGLT2 inhibitors, which induce osmotic diuresis, a triple combination of RAS/SGLT2 inhibitors plus a MRA may be particularly potent to maximize organ protection and minimize the risk of hyperkalemia, an evolving hypothesis to be tested in a clinical trial.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Cidlowski, et al., 2021; Alexander, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Buneman, et al., 2021; Alexander, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, et al., 2021).

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Figure Legends

Figure 1. Overview of the causes of CKD and the therapeutic options along the CKD progression timeline. Despite having different etiologies, glomerular and tubulointerstitial CKD both share nephron loss and fibrosis, leading to atrophy and renal dysfunction. When the origin of CKD is known, specific therapy against the original disease can be given. RAS and SGLT2 inhibitors represent the standard of care to slow CKD progression. The blockade of inflammation and fibrosis (e.g., with MRAs) could have an additional nephroprotective effect. As cardiovascular (CV) risk increases as renal dysfunction worsens, the control of CV risk is essential in CKD patients.

Figure 2. Experimental and clinical evidence for a benefit of MRAs in renal diseases. MRAs show direct beneficial effects on renal function in several experimental models of kidney disease and clinical trials have yielded positive results in renal outcomes in diabetic and non-diabetic CKD. An additional reduction in cardiovascular risk has also been reported in several experimental and clinical studies.

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