International Journal of Cardiology 200 (2015) 20–24

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

The renal effects of mineralocorticoid receptor antagonists☆

Stefano Bianchi [a,*], Valentina Batini [b], Roberto Bigazzi [b]

[a] Unità Operativa di Nefrologia e Dialisi II, Livorno, Italy
[b] Dipartimento di Medicina Clinica ed Unità Operativa di Nefrologia e Dialisi I, Livorno, Italy

ARTICLE INFO

Article history:
Received 4 December 2014
Accepted 17 May 2015
Available online 22 May 2015

Keywords:
Chronic kidney disease
Mineralocorticoid receptor antagonists
Glomerular filtration rate
Proteinuria
Hyperkalemia

ABSTRACT

Beyond its well known classic effects on renal water and electrolytes metabolism, an increasing amount of experimental and clinical evidence suggests that aldosterone contributes to the pathogenesis and progression of kidney disease. The binding of aldosterone on epithelial and non-epithelial cells of the kidney induces many deleterious effects, such as podocyte apoptosis and injury, mesangial cell proliferation and deformability and tubulointerstitial inflammation, finally resulting in glomerular fibrosis and sclerosis. Moreover, aldosterone acting by fast non-genomic mechanisms, may induce other potential deleterious effects on kidney function and structure. Indeed, many experimental studies have shown that aldosterone participates to the progression of kidney disease through hemodynamic and direct cellular actions and that antagonists of aldosterone may retard the progression of kidney disease, independently of effects on blood pressure. Therefore, blockade of the aldosterone pathway may prove to be a beneficial therapy for kidney disease.
In this brief review we summarize the reported data that support an independent role of aldosterone in inducing kidney damage both in human and experimental models, and interventional studies that highlight how strategies aimed to antagonize its action may favorably modify the progressive decline of renal function in patient with kidney disease and in patients with extrarenal disease frequently associated with kidney function impairment.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Aldosterone action, after its release from the zona glomerulosa of the adrenal gland, was believed since its isolation and characterization more than 50 years ago [1] to be limited to just few classical target organs, mainly of epithelial origin (kidney, colon and salivary and sweat glands), where the hormone induces the biochemical modifications required to maintain volume and electrolyte homeostasis by acting through genomic pathways. Targeting the tubular cells of the distal nefron of the kidney, aldosterone increases sodium reabsorption by binding to the intracellular mineralocorticoid receptor (MR) that translocates to the nucleus, where it upregulates the transcription of genes encoding Na/K-ATPase and epithelial sodium channel subunits. In the end, aldosterone promotes volume expansion, thereby increasing blood pressure.

Recently however, this historical view has been modified, leading to a better understanding of the multitude of effects of aldosterone on the kidney, besides the classical effects on sodium and potassium transport in the renal tubules. MR, which mediates the genomic effects of aldosterone, is expressed in many other residing cells of the kidney. In fact it occurs also in podocytes, mesangial cells, fibroblasts, endothelial cells, etc. [2]. Binding of aldosterone to MR affects negatively the physiology of all the above cells by inducing podocyte apoptosis, mesangial proliferation and deformability, finally resulting in inflammation, fibrosis and sclerosis of the glomerular and interstitial structure [3]. On the other hand, MR blockade by MR antagonist (MRA) induces a remission of glomerulosclerosis [4] and decreases cardiac hypertrophy in a chronic kidney disease (CKD) model [5]. Furthermore, aldosterone is also synthetized in many extraadrenal tissues, including the kidney [6,7]. It is also likely that aldosterone acts in a paracrine fashion and by rapid non-genomic mechanisms [8].

Considered for years solely as a friendly 'renal hormone', aldosterone is now recognized as a key player in many pathological conditions, such as cardiovascular and kidney diseases, hypertension, metabolic syndrome, etc. The recognition of its direct effect on renal hemodynamic, inflammation, fibrogenesis, endothelial function, fibrinolysis and oxidative stress supports a broader implication of aldosterone than previously anticipated.

2. Most harmful effects of renin–angiotensin–aldosterone system on the kidney are mediated by aldosterone and abrogated by MRA

There is great amount of evidence that renin–angiotensin–aldosterone system (RAAS) plays an important role in the pathogenesis and progression of renal diseases. Blockade of RAAS through angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker

☆ Authorship: All authors had access to and participated in writing this manuscript.
* Corresponding author at: Via Roberto Bracco, 1, 57127 Livorno, Italy.
E-mail address: s.bianchi@usl6.toscana.it (S. Bianchi).

http://dx.doi.org/10.1016/j.ijcard.2015.05.125
0167-5273/© 2015 Elsevier Ireland Ltd. All rights reserved.

(ARB) is considered the most effective therapy in slowing progression of CKD. ACEi and ARB, however, provide only imperfect protection since they sometimes fail to prevent end-stage renal failure [9]. Moreover, ACEi and ARB reduce effectively aldosterone levels during acute therapy, while the suppression of aldosterone is variable and unsustained over the long term treatment. It is possible that RAAS inhibition strategies may be suboptimal, because serum aldosterone levels may increase during RAAS blockade with ACEi or ARB (aldosterone breakthrough). This phenomenon may be associated with more severe renal damage and seems to be independent of the RAAS inhibition dosage. Although angiotensin II has been identified as the primary mediator of the system, many recent studies have raised the possibility that aldosterone, independent of renin–angiotensin, contributes in mediating renal injury.

Indeed, CKD is characterized by elevated levels of aldosterone, and this has been demonstrated both in animals [10] and humans [11,12]. In rats with subtotal nephrectomy and adrenalectomy, proteinuria, hypertension and structural renal injury were less pronounced than in rats with intact adrenal glands [13]. A causal role of aldosterone in CKD is also indicated by the findings reported by Quinkler et al. [14] on kidney biopsies of patients with CKD. Serum aldosterone was correlated negatively with creatinine clearance and positively with renal scarring, and in the biopsies of patients with higher proteinuria, the MR was increased 5-fold. In a study performed in the general Japanese population, normotensive individuals without any sign of kidney disease were followed for more than 9 years [15]. Adverse renal outcome was predicted by a higher baseline aldosterone-to-renin ratio. Similarly, the prospective Framingham offspring study [16] showed that the baseline aldosterone concentration in healthy individuals was significantly associated with the development of CKD during follow-up.

Green and collaborators [10] have attracted renewed attention to the role of aldosterone as independent cause of renal damage. In 1996 they demonstrated that aldosterone was able to reverse the renal protective effects of RAAS blockade in the 5/6 nephrectomy rat. They found that pharmacologic blockade of RAAS with ARB, which was associated with suppression of aldosterone secretion, reduces proteinuria and renal lesions, all of which were almost completely reversed when aldosterone was infused concurrently. Rocha et al. also demonstrated that renal-protective effects of ACEi were reversed by the infusion of aldosterone in stroke-prone spontaneously hypertensive rat. The authors found that treatment with captopril prevented the development of proteinuria and glomerular sclerosis while reducing endogenous aldosterone levels, whereas subsequent aldosterone infusion reversed almost completely these protective effects of captopril [17]. Shibata and collaborators demonstrated that uninephrectomized rats, treated with exogenous aldosterone infusion for weeks, exhibited higher proteinuria than control rats and reduced expression of nephrin, a transmembrane protein of the slit diaphragm, with consequent significative glomerular damage. Such injury was prevented by treatment with the MRA eplerenone [3] [Table 1]. The prevention of kidney injury by the administation of MRA in animal model of hypertension [18], nephron reduction [4] and diabetes [19] suggests the significant involvement of MR in these pathophysiological processes.

Therefore, aldosterone may contribute to renal impairment via direct and indirect effects. Direct effects are mediated through the MR by causing tubulointerstitial inflammation and subsequent fibrosis. Indirect effects could be the consequence of non-genomic effect of this hormone (Fig. 1). Aldosterone exerts deleterious renal hemodynamic effects by elevating renal vascular resistance and glomerular capillary pressure, two conditions that have been demonstrated to cause proteinuria and accelerated kidney injury. Rising doses of aldosterone in rabbits cause dose-dependent constriction in both arterioles, with a higher sensitivity in efferent arterioles. The result is an increase of intraglomerular pressure with consequent proteinuria and renal damage. These vasoconstrictor actions are presumably non-genomic since maximum reduction of the arteriole's lumen happens in less than 10 min [8]. Furthermore it has been shown that the infusion of aldosterone for 1 week to normotensive dogs determined a 20% to 24% increase of glomerular filtration rate (GFR), which was associated with an increase of renal perfusion pressure [20]. In all, these studies suggest that MRA may reduce GFR, at least acutely, due to direct effects on the renal microcirculation.

Table 1
Potential beneficial effects of mineralocorticoid receptor antagonists on kidney function and structure.

↓ Glomerular podocyte injury
↑ Glomerular expressions of slit diaphragm–associated molecules (nephrin and podocin)
↓ Desmin, a damaged podocyte marker
↓ Monocyte and macrophage infiltration
↓ Tubulointerstitial inflammation and fibrosis
↓ Plasminogen activator inhibitor-1 and transforming growth factor-β1
↓ Connective tissue growth factor
↓ Proinflammatory cytokines (osteopontin and monocyte chemoattractant protein-1)
↓ Vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1)
↓ Reactive oxygen species production
Vasodilatation or pre-glomerular afferent and mostly post-glomerular efferent arterioles
↓ Intraglomerular pressure and glomerular filtration rate (acute effect)
Stabilization of glomerular filtration rate (long-term effect)
↓ Proteinuria (acute and long-term effect)

3. Effects of MRA in patients with chronic kidney disease

There is an increasing amount of evidence indicating that aldosterone can induce renal damage also in humans and this hypothesis was first postulated since the description of the syndrome characterized by excess of aldosterone synthesis. In 1964 Conn et al. in the reported study of 145 patients with primary hyperaldosteronism, a condition characterized by excessive and largely autonomous aldosterone secretion, showed that high plasma aldosterone levels were in most cases associated with proteinuria and reduced renal function. For some time these renal symptoms have been attributed only to the deleterious effects of high blood pressure rather than to the direct effects of aldosterone on renal function and structure [21]. A higher prevalence of proteinuria and renal damage has been recently confirmed in patients with primary aldosteronism [22]. These conditions were significantly ameliorated after treatment with MRA [23].

On the basis of the effect of aldosterone in inducing kidney damage and the potential role of MRA in antagonizing these negative effects, recent interest has developed in therapeutic strategy aimed to reduce proteinuria and retard the progression of CKD by using MRA. Aldosterone has become a therapeutic target in patients with CKD since the publication in 2001 of the paper of Chrysostomou et al. In an uncontrolled study, these authors reported that the addition of spironolactone to ACEi in a small group of proteinuric patients with CKD induced a dramatic reduction of proteinuria, without any negative effects on renal function [24]. In a short-term study, Bianchi et al. observed that spironolactone effectively reduced proteinuria in non-diabetic CKD patients, already treated with ACEi and/or ARB, after only two weeks of treatment. It is noteworthy that in this study baseline levels of aldosterone were significantly correlated with the degree of reduction in proteinuria [25]. In diabetic patients with CKD and high levels of aldosterone, notwithstanding an active treatment with ACEi, Sato et al. [26] reported a significant reduction of proteinuria after 24 weeks of treatment with spironolactone. Of note, the decrease of proteinuria was more pronounced among patients with aldosterone breakthrough. The effect of spironolactone in decreasing proteinuria has been observed to persist 6–12 months in patients with CKD on long-term therapy with ACEi and/or ARB [12,27,28].

Similar findings were observed in studies that have used the more selective MRA eplerenone. Epstein et al. showed that eplerenone reduced proteinuria more effectively than an ACEi in patients with type

Download English Version:

https://daneshyari.com/en/article/2928889

Download Persian Version:

https://daneshyari.com/article/2928889

Daneshyari.com