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Mineralocorticoid receptor antagonist in heart failure: Past, present and future perspectives

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ABSTRACT

Aldosterone is involved in various deleterious effects on the cardiovascular system, including sodium and fluid retention, myocardial fibrosis, vascular stiffening, endothelial dysfunction, catecholamine release and stimulation of cardiac arrhythmias. Therefore, aldosterone receptor blockade may have several potential benefits in patients with cardiovascular disease. Mineralocorticoid receptor antagonists (MRAs) have been shown to prevent many of the maladaptive effects of aldosterone, in particular among patients with heart failure (HF). Randomized controlled trials have demonstrated efficacy of MRA in heart failure with reduced ejection fraction, both in patients with NYHA functional classes III and IV and in asymptomatic and mildly symptomatic patients (NYHA classes I and II). Recent data in patients with heart failure with preserved ejection fraction are encouraging. MRA could also have anti-arrhythmic effects on atrial and ventricular arrhythmias and may be helpful in patient ischemic heart disease through prevention of myocardial fibrosis and vascular damage. This article aims to discuss the pathophysiological effects of aldosterone in patients with cardiovascular disease and to review the current data that support the use of MRA in heart failure.

1. Aldosterone in the pathophysiology of heart failure

Aldosterone is a mineralocorticoid hormone produced in response to angiotensin II release, hyperkalemia, and corticotropin mainly by the adrenal cortex. In addition to this pathway, recent evidences suggest local, extra-adrenal production of aldosterone by endothelial cells and vascular smooth muscle cells in the blood vessels and myocardium [1,2].

Aldosterone binding to mineralocorticoid receptor results in reabsorption of sodium and water in exchange for potassium in various sites including the distal tubule and collecting duct of the nephron, causing an increased intravascular fluid retention and volume overload. In addition to these classical epithelial effects, aldosterone has a variety of negative non-epithelial effects including induction of inflammation, vascular stiffening, collagen formation, myocardial necrosis and stimulation of fibrosis [1].

Aldosterone has an important role in the pathogenesis of heart failure. Increased levels of aldosterone tend to promote myocardial hypertrophy and remodeling, induce fibrosis and apoptosis, contribute to endothelial dysfunction and reduce myocardial perfusion, thus increasing the incidence of cardiovascular events [3]. In patients with HF, plasma aldosterone may reach levels of 300 ng/dL, which is up to 60-fold the levels measured in normal subjects (5–15 ng/dL) [1].

Aldosterone has well-known effects in sodium and fluid retention that could account for an undesired impact in fluid balance in patients with CHF, causing hypervolemia and promoting congestion. In addition to its role in sodium balance, aldosterone stimulates cardiac fibrosis, which is one of the principal mechanisms involved in cardiac remodeling and progression of heart failure. In experimental models stimulation of mineralocorticoid receptor has been found to increase cardiac levels of the matrix cellular protein osteopontin, leading to increased fibrosis, and diastolic dysfunction [4].

Other studies have shown an increase of collagen and fibrosis in myocardial tissue in subjects treated with aldosterone [5–7]. Mechanisms at the basis of this action are various. Lijnen et al. proposed an involvement of angiotensin II acting through up-regulation of angiotensin receptor subtype 1 induced by aldosterone [8]. At a molecular level, Nakamura et al. demonstrated a critical role of apoptosis signal-regulating kinase 1 (ASK1) in the mechanism underlying aldosterone-induced cardiac injury. ASK1 is implicated in aldosterone/salt-induced cardiac inflammation and fibrosis through the enhancement of NADPH oxidase-mediated oxidative stress and the up-regulation of the cardiac renin–angiotensin system [9]. Aldosterone also enhances the gene expression of profibrotic molecules, including collagen, transforming growth factor-beta (TGF-beta) and plasminogen activator inhibitor,

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type 1 (PAI1). Aldosterone can also exert rapid, non-genomic effects, which involve transactivation of the epithelial growth-factor receptor (EGFR) and the phosphorylation of extracellular-signal-regulated kinase 1 (ERK)1/ERK2, thereby up-regulating the expression of pro-inflammatory transcription factors and related molecules. In the myocardium and in the kidney, the net effect of aldosterone-induced inflammation and extracellular matrix accumulation is tissue fibrosis and, ultimately, myocardial and renal scarring [10].

Another consequence of aldosterone/MR activation and cardiac remodeling is electrical remodeling. Myocardial fibrosis induced by aldosterone has an arrhythmogenic role in heart failure [11–13]. Some studies confirm that aldosterone and MR activation have also direct effects on cardiomyocyte calcium-handling that may predispose to arrhythmias [14].

Aldosterone is also involved in endothelial dysfunction, mainly by decreasing the bioavailability of nitric oxide and promoting oxidative stress [16].

Other negative effects of aldosterone are activation of the sympathetic nervous system, reduction of baroreceptor sensitivity, and activation of myocyte apoptosis [2].

Given these assumptions, it is clear that aldosterone receptor blockade could be beneficial in patients with cardiovascular disease in a variety of ways. Aldosterone receptor antagonists have been shown to prevent many of the maladaptive effects of aldosterone on the cardiovascular system. For instance, spironolactone prevents the aldosterone-mediated collagen synthesis that contributes to adverse left ventricular remodeling [7]. Rats with post-infarction heart failure treated with aldosterone receptor antagonists have improved left ventricular (LV) diastolic and systolic functions, a reduction of reactive fibrosis, and reduced myocardial norepinephrine content [17]. Eplerenone inhibits superoxide formation and enhances nitric oxide-dependent relaxation in experimental studies [18].

2. Aldosterone receptor antagonists

2.1. Spironolactone

Spironolactone is a widely used, non-selective aldosterone receptor antagonist marketed since the early 60s that is metabolized extensively in the liver to its active metabolites. Its plasma half-life is 1.4 h, although in CHF patients with hepatic congestion, this duration may increase 5-fold. A maximal drug response is seen 48 h after the first dose. Spironolactone is structurally similar to progesterone, thereby allowing sex-steroid receptor cross-reactivity. This phenomenon accounts for the anti-progesterone and anti-androgen effects observed in some patients treated with spironolactone. Gynecomastia or breast pain is the most frequent side-effect of spironolactone, occurring in about 10% of patients in chronic treatment [19].

2.2. Canrenone

Canrenone is the principal active metabolite of spironolactone, devoid of first-pass effect, and has a long half-life (of 16.5 h). As spironolactone, canrenone is a non-selective MRA, but a lower incidence of anti-androgen side effects has been reported [20]. It is frequently used as an alternative to spironolactone mainly in European countries. Canrenone is also derived from the rapid conversion in vivo of the salt potassium canrenoate, which has shown important anti-remodeling effects in post-infarction LV remodeling [21].

2.3. Eplerenone

Eplerenone is a selective aldosterone receptor antagonist derived from spironolactone but with lower affinity for the progesterone and androgen receptors so it lacks sex-related adverse side effects. Eplerenone is metabolized in the liver by cytochrome P450 (isoenzyme CYP3A4); plasma levels of eplerenone are influenced by concomitant use of inhibitors of CYP3A4, including ketoconazole, itraconazole, ribonavir, and clarithromycin, that are associated with significant increases in its peak levels, whereas inducers of CYP3A4 such as phenobarbital decrease it. Eplerenone has a plasma half-life of 4 to 6 h, and steady-state drug levels are usually achieved 48 h after the first dose.

2.4. Side effects

A serious class side effect of MRAs is represented by hyperkalemia. Aldosterone, by binding its receptor, stimulates the apical Na–K-ATPase pump and luminal potassium channel activity into the late distal convoluted tubules and the distal collecting ducts, thus promoting luminal potassium excretion. Therefore, antagonism of the aldosterone receptor decreases luminal K excretion, promoting accretion of potassium in the body. When severe, hyperkalemia may precipitate cardiomyocyte membrane potential destabilization and unstable ventricular arrhythmias [17]. Although serious hyperkalemia occurred in about 2–3% of MRA treated patients in randomized clinical trial, [19,22] rates as high as 10% in the community have been reported [18]. The risk of serious hyperkalemia is minimized by routine serum potassium and renal function monitoring, and avoidance of concurrent pharmacotherapies associated with potassium retention or diet and dietary supplements containing high levels of potassium. Of particular interest, a novel therapeutic agent called RLY5016 (oral, a non-absorbed, potassium-binding polymer) prevented hyperkalemia in patients with HF receiving standard therapy and spironolactone [23].

Other important side-effects are linked to spironolactone cross-reaction with androgen-receptors. The incidence of spironolactone-associated breast tenderness and gynecomastia reported in clinical trials is 6.9% to 10% for men and typically occurs at doses 50 mg/d [19]. Generally, these side effects resolve with drug cessation. Spironolactone may also lower testosterone levels, causing erectile dysfunction in male and menstrual irregularities in female; when present, these side effects increase rates of medication noncompliance [7]. In contrast to spironolactone, eplerenone has 100–1000 lower affinity to testosterone and progesterone receptors, meaning less pronounced, placebo-equivalent, sexual side effects [22].

2.5. Future research on aldosterone antagonists and synthase inhibitors

There is an active research for novel aldosterone antagonists with similar potency as spironolactone and even higher specificity than eplerenone such as SM-368229 from Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan) [24]. A novel approach is to move from receptor blockade to the inhibition of aldosterone synthesis [25]. At least three compounds with this mechanism of action were identified: FAD286 (Novartis, Basel, Switzerland), LCI699 (Novartis, Basel, Switzerland) and SPP2745 (Novartis, Basel, Switzerland) [26]. FAD286, an enantiomer of fadrazole with an inhibitory effect on aldosterone synthase, has been shown to reduce blood pressure, attenuate myocardial and renal injury [27,28] and normalize redox status in rats after myocardial infarction [29]. SPP2745 suppressed aldosterone levels and also provided cardiac, renal and vascular protective effects when administered on top of conventional therapy [26]. Finally, LCI699 suppressed aldosterone levels and lowered blood pressure by 4.1 mm Hg in 14 hypertensive patients, but also latently inhibited cortisone formation [30]. Inhibition of aldosterone synthase should prevent reactive increase in aldosterone levels and adverse androgen receptor-related effects, since these new drugs do not have a steroid structure. On the other hand, mineralocorticoid receptors are also stimulated by cortisol and other ligands that are released in conditions of augmented oxidative stress [31]. Aldosterone synthase inhibitors will not oppose these aldosterone-independent mechanisms that might be blocked by spironolactone or eplerenone. Future studies will show whether what these theoretical concerns will have as clinical implications.