Aldosterone and Its Role In Progression of Kidney And Cardiovascular Disease.

Essay
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Introduction

Worldwide, more than 60 million individuals are estimated to have some degree of chronic kidney disease (CKD)and the burden might double in the next 10 years (Remuzzi and Weening, **2005**).

Aldosterone is a potent mineralocorticoid which regulates body fluids' electrolyte balance by promoting potassium elimination and sodium retention (Rocha and Williams, **2002**).

Aldosterone is produced in the zona glomerulosa layer of the adrenal cortex. It is also produced in endothelial and vascular smooth muscle cells in the heart, blood vessels, and brain. Aldosterone acts through epithelial mineralocorticoid receptors in the kidney, cardiovascular system, and other organs. Aldosterone plays a major role in salt and water homeostasis and potassium excretion, and mediates renal and vascular remodeling (Hostetter, **2004**).

In recent years, it has been clarified that The renin-angiotensin-aldosterone system (RAAS) plays a major role in the pathogenesis of CKD. After its release from the zona

glomerulosa of the adrenal gland, aldosterone mediates the insertion of epithelial sodium channels in the collecting duct of the nephron and reabsorption of sodium and water. In instances of aldosterone hyperactivity, systemic hypertension can develop secondary to increased volume and salt reabsorption, leading to an increase in glomerular hydrostatic pressure, progressive glomerulosclerosis, increased afterload, and left ventricular dysfunction(Kotchen, **2011**).

Aldosterone Induces inflammation and fibrosis in the heart, vasculature andKidney (Brown, **2008**).

Additionally, aldosterone may contribute to end organ damage by enhancing the proinflammatory effects of angiotensin II (Lea et al., **2009**).

More than 10 years ago,it was demonstrated that aldosterone contributed to proteinuria and glomerular injury in the remnant kidney model (Ciraku et al., **2000**).

Aldosterone infusion induces proteinuria by Potentiation of angiotensin II (Ang II) that mediates potent constriction of more renal efferent than afferent arterioles causes glomerular hyperfiltration leading to proteinuria (Arima et al., **2003**).

Chronic kidney disease (CKD) is a major public health problem, and preventing CKD and/or delaying progression of CKD patients to end-stage renal disease (ESRD) is a major task for the nephrology community (Schieppati and Remuzzi , **2003**).

This looked like an achievable target, in particular because of the availability of renoprotective drugs that may interfere with disease progression such as the inhibitors of the renin - angiotensin-aldosterone system (RAAS) (Smith and Vane, **2003**).

Other drugs have become progressively available that interfere With RAAS activity, such as AII-type 1 receptor blockers (ARBs) and the aldosterone antagonists that inhibit AII and Aldos activity by competitively antagonizing their binding to specific receptors (Zaman et al., **2002**).

Aldosterone blockade has been shown to be effective in reducing total mortality as well as cardiovascular mortality/ cardiovascular hospitalizations in patients with systolic left ventricular dysfunction (SLVD) with chronic heart failure due to an ischemic or non-ischemic etiology as well as in patients

post acute myocardial infarction with SLVD (Pitt et al., **2003**).

Although spironolactone is an effective anti-aldosterone agent, its widespread use in humans is limited by its tendency to produce undesirable sexual side-effects. At standard doses, impotence and gynecomastia can be induced in men, whereas pre-menopausal women may experience menstrual disturbances. These adverse effects are due to the binding of spironolactone to progesterone and androgen receptors and are a substantial cause of drug discontinuation (Mantero et al., **1995**).

Spironolactone has a very high degree of first pass metabolism in man with metabolites that undergo a high degree of enterohepatic cycling (Abshagen et al., **1977**).

Spironolactone is also an inducer of hepatic microsomal drug metabolizing enzymes in man (Overdiek and H.W, **1987**).

A new aldosterone receptor antagonist, eplerenone, has been recently marketed. It is a molecule in which the 17_-thioacetyl group of spironolactone is replaced by a 9,11-epoxy moiety that confers excellent selectivity for the aldosterone receptors

and decreases the affinity for other renal and extrarenal (such as testis)steroid receptors.This avoids the side effects, such as impotence, gynecomastia or menstrual disturbances ,characteristic of the nonselective antagonists (Calhoun , **2006**).

Zannad et al report the efficacy of eplerenone in reducing the risk of death from cardiovascular causes, as compared with placebo . The primary route of elimination for eplerenone is via cytochrome P450 (CYP) 3A4-mediated metabolism (Zannad et al., **2011**).

Both eplerenone and spironolactone are associated with dose-related increases in serum potassium levels (McMurray and O'Meara, **2004**).

Patients with underlying renal dysfunction or heart failure are at greatest risk of hyperkalemia (Sica, **2005**).

It has been speculated that the extended half-life of the active metabolites of spironolactone could increase the risk of hyperkalemia or its associated complications (Sica, **2005**).

Conversely, the relatively short half-life of eplerenone and that it has active metabolites,may lessen the risk of hyperkalemia (Tamirisa et al., **2004**).

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Table of content