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Efficacy and safety of mineralocorticoid receptors in mild to moderate arterial hypertension

Francesco Pelliccia [a,*], Giuseppe Rosano [b,c], Giuseppe Patti [d], Maurizio Volterrani [b], Cesare Greco [a], Carlo Gaudio [a,e]

[a] Department 'Attilio Reale', Sapienza University, Rome, Italy
[b] IRCCS San Raffaele Pisana, Rome, Italy
[c] Cardiovascular and Cell Sciences Research Institute, St. George's, University of London, London, UK
[d] Campus Biomedico, Rome, Italy
[e] Eleonora Lorillard Spencer Cenci Foundation, Rome, Italy

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ABSTRACT

The mineralocorticoid receptor antagonists have been shown to have favourable safety and cost-effectiveness profiles across a broad range of clinical indications, including heart failure, primary aldosteronism and resistant hypertension. The clinical biology of the first aldosterone blocker, i.e. spironolactone, and its effects in several organ systems has been well elucidated from multiple studies. The range of adverse effects experienced with spironolactone has led to its modification and the consequent synthesis of eplerenone. Scientific evidence accumulated so far supports the role of eplerenone as first-choice drug in heart failure, with lower prevalence rates of sex-related adverse effects associated with eplerenone as compared to spironolactone. In Europe, eplerenone is currently marketed only in some countries and only with the indication of heart failure, whereas its clinical efficacy and safety in mild to moderate hypertension is said to be uncertain. A review of available scientific evidence, however, discloses that 11 randomized clinical trials assessing eplerenone in >3500 hypertensives have been reported so far. The results of these studies clearly show that eplerenone is an effective antihypertensive agent when used alone or in combination with other medications. In doses ranging from 25 to 100 mg daily, eplerenone monotherapy results in a dose-dependent reduction in clinic blood pressure. As compared to placebo, eplerenone reduces significantly blood pressure from baseline. In general, 100 mg daily eplerenone has a blood pressure lowering that is 50 to 75% that of spironolactone. Eplerenone results in a greater reduction in blood pressure as compared with losartan, and comparison between eplerenone and amlodipine shows that both treatments decrease systolic blood pressure to a similar extent but eplerenone is better tolerated. In conclusion, there is now evidence that eplerenone can play an important role in the treatment of mild to moderate arterial hypertension and therefore scientific experts and regulatory authorities should support its wider use in clinical practice worldwide.

1. Introduction

Hypertension is one of the most important preventable causes of premature morbidity and mortality worldwide. Indeed, it is a major risk factor for ischaemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease and cognitive decline [1]. Indeed, arterial hypertension can lead to left ventricular hypertrophy and remodelling of resistance arteries, both of which are associated with adverse cardiovascular outcomes [2]. Most cases of hypertension have no known cause and are termed essential hypertension. Secondary causes of hypertension account for approximately 10% of cases, and treatment of secondary hypertension generally involves treating the underlying cause [2]. Whatever the aetiology, it is clear that controlling high arterial pressure improves life expectancy and is an important component of primary prevention of cardiovascular disease.

2. The clinical biology of aldosterone in hypertension

The renin–angiotensin–aldosterone system plays an essential role in blood pressure control through regulation of fluid and electrolyte balance [3]. Angiotensin II, i.e. the main effector of the renin–angiotensin system, acts on the type I angiotensin II receptor thus increasing blood pressure by a combination of vasoconstriction, increased cardiac output, vascular remodelling and increased aldosterone secretion. Aldosterone plays an important role in electrolyte homeostasis. It acts on mineralocorticoid receptors in the cortical collecting ducts of the kidney to increase expression of sodium channels, thus leading to sodium and water reabsorption, increase in plasma volume, and a consequent rise in blood pressure [4].

* Corresponding author at: Via Tommaso Inghirami 85, 00179 Rome, Italy.
E-mail address: f.pelliccia@mclink.it (F. Pelliccia).

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The role of aldosterone in hypertension was first recognised in 1954 by Conn and Louis, who treated a case of hypertension by removal of an adrenal adenoma which secreted excess aldosterone. Subsequent work has clearly demonstrated that aldosterone also plays an important role in hypertension in the absence of primary aldosteronism [5]. Indeed, 15% of hypertensive patients and 25% of those with resistant hypertension have an abnormally high aldosterone/renin ratio, and higher 24-hour urinary aldosterone levels can be found in patients with untreated hypertension as compared to patients with controlled hypertension [5].

The effects of aldosterone are more widespread than simply regulating sodium and potassium levels [6]. Mineralocorticoid receptors are found in a large range of tissues including adipose cells, cardiac myocytes, vascular endothelium, cardiac fibroblasts and vascular smooth muscle cells [6]. Aldosterone activation of mineralocorticoid receptors leads to upregulation of NADPH oxidase which in turn increases the production of reactive oxygen species. The generation of reactive oxygen species causes a reduced bioavailability of nitric oxide, which is associated with impaired relaxation of vascular smooth muscle cells, thereby leading to increased peripheral vascular resistance and higher blood pressure. Furthermore, lower nitric oxide levels are associated with endothelial dysfunction and increased expression of cell adhesion molecules which increases the risk of atherosclerosis.

Along with the well-recognised effects on blood pressure (the so-called 'genomic effects' of aldosterone), several lines of evidence indicate that aldosterone promotes its deleterious effects on target organs independently of blood pressure (the so-called 'nongenomic effects') [7,8]. As a matter of fact, aldosterone acts directly on the endothelial cell and the vasculature, and pathophysiologic and outcome studies suggest a rationale for aldosterone blockade as prevention or reversal of organ damages in the heart, kidneys, and vasculature (Fig. 1). In experimental models, aldosterone blockade attenuates cardiac fibrosis in the damaged heart, reduces aortic fibrosis, and improves both large artery compliance and endothelial function. Clinical trials have shown that spironolactone reduces cardiac and vascular collagen turnover, improves reflex control, reduces ventricular arrhythmias, and dilates blood vessels [9]. These hemodynamic and humoral actions of aldosterone may translate into specific clinical benefits in hypertension and cardiovascular and renal diseases. Also, extensive preclinical and clinical evidence supports the efficacy of mineralocorticoid receptor antagonists in attenuating proteinuria [10]. These data are consistent with the concept that mineralocorticoid receptor activation promotes renal injury, and therefore add-on aldosterone blockade should be viewed as an effective strategy for attenuating renal injury [11].

3. Mineralocorticoid receptor antagonism in hypertension: initial experiences

The effects of aldosterone on sodium retention and the importance of sodium restriction in blood pressure regulation has been the background for assessing the therapeutic role of agents able to block the mineralocorticoid receptors in arterial hypertension.

Mineralocorticoid receptor antagonists provide effective antihypertensive treatment in most patients with low renin forms of hypertension, particularly in blacks, elderly patients, and diabetics [11,12]. Mineralocorticoid receptor antagonists are also effective in the large subgroup of individuals with the metabolic syndrome (obesity, hypertension, insulin resistance, dyslipidemia, accelerated atherogenesis) [13]. On the basis of available scientific evidence, therefore, the majority of hypertensive patients can be expected to have some level of response to mineralocorticoid receptor antagonists.

Originally, aldosterone blockade with spironolactone assumed an important role in the treatment of resistant hypertension, defined as failure to achieve target blood pressure despite treatment with ≥3 medications. Recent clinical studies also indicate that aldosterone blockade provides significant incremental blood pressure reduction when added to treatment regimens of patients with resistant hypertension [14]. In general, the combined use of a mineralocorticoid receptor antagonist and adequate doses of a diuretic, e.g. chlorthalidone, is recommended for the treatment of resistant hypertension in order to maximize the therapeutic response and reduce risk of hyperkalemia.

4. Spironolactone as antihypertensive agent

The first mineralocorticoid receptor antagonist used in hypertension was spironolactone, which was introduced in 1960 and still remains commonly used 50 years later [15]. Spironolactone acts in the aldosterone-sensitive distal tubular site of the nephron by indirect inhibition of sodium reabsorption through the epithelial sodium channel

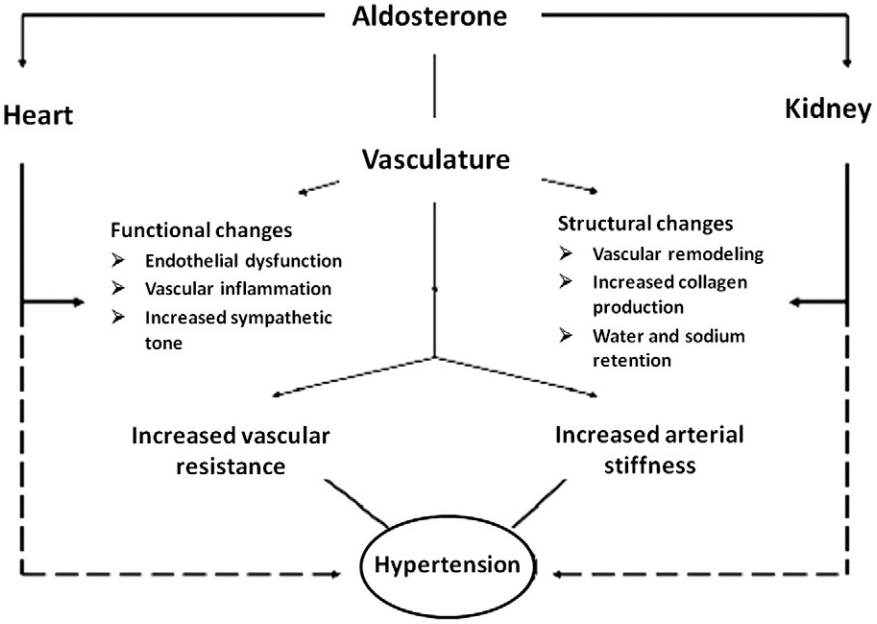

Fig. 1. Aldosterone may directly mediate its detrimental effects in the heart, kidney and vasculature through mineralocorticoid receptors. Indeed, aldosterone increases vascular tone due to endothelial dysfunction and upregulates angiotensin II receptors. In addition, it causes vascular remodelling of small and large arteries, promotes collagen synthesis, and determines water and sodium retention. These abnormalities eventually lead to increased arterial stiffness and elevation of blood pressure.