Aldosterone and anti-aldosterone effects in cardiovascular diseases and diabetic nephropathy

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SUMMARY
Cells in the cortical collecting duct of distal nephron have been considered for a long time as the unique cellular targets of aldosterone. However, it is now clear that other cell types in non-epithelial tissues are also potential targets for aldosterone. The functions that this hormone controls in non-epithelial tissues are still a matter of debate. Clinical and experimental studies have established that aldosterone plays a major role in the pathophysiology of cardiovascular and renal diseases. The aldosterone receptor antagonists spironolactone and eplerenone have demonstrated specific effects not related to their hypotensive properties in hypertension or cardiac diseases. It appears that a key action of these molecules is related to prevention or treatment of end-organ damage. The latter fact, and the recognition of aldosterone escape on long-term treatment of heart failure, diabetic nephropathy and some forms of hypertension with ACE inhibitors, justify the clinical use of aldosterone receptor antagonists. Clinical studies have allowed to draw a still incomplete but comprehensive scheme of aldosterone cardiovascular actions in pathological conditions. When elevated, aldosterone has deleterious effects in blood vessels, the heart and in kidney, which are secondary to the induction of inflammatory and oxidative processes and necrosis, that induce the increased synthesis of extracellular matrix proteins.

Key-words: Aldosterone · Renin-angiotensin system · Heart failure · Diabetic nephropathy · Cardiac hormones.

Résumé
Effets de l’aldostérone et des anti-aldostérones dans les maladies cardiovasculaires et la néphropathie diabétique
Les cellules du tubule distal du néphron ont longtemps été considérées comme les seules cibles cellulaires de l’aldostérone. S’il est maintenant établi que d’autres types de cellules non épithéliales sont des cibles possibles, les fonctions que l’aldostérone contrôle dans ces tissus sont encore débattues. Les études expérimentales et cliniques ont établi que l’aldostérone joue un rôle déterminant dans la patho-physiologie des maladies cardio-vasculaires et rénales. Les antagonistes du récepteur de l’aldostérone ont montré des effets non liés à leurs propriétés anti-hypertensives. Il apparaît, en fait, qu’une action clé de ces molécules est en lien avec la prévention ou le traitement des organes cibles. Ce dernier fait, ainsi que la reconnaissance d’un échappement de l’aldostérone dans le traitement au long cours de certaines formes d’hypertension, de l’insuffisance cardiaque et de la néphropathie diabétique, justifient l’utilisation clinique des antagonistes du récepteur de l’aldostérone. Les études expérimentales ont permis de tracer les grandes lignes des actions cardiovasculaires de l’aldostérone en conditions pathologiques. À concentration élevée, l’aldostérone a des effets délétères sur les vaisseaux, le cœur et le rein, secondaires à l’induction de processus inflammatoires et oxydatifs et de nécrose, qui entraînent la stimulation des constituents de la matrice extracellulaire.

Mots-clés : Aldostérone · Système rénine-angiotensine · Insuffisance cardiaque · Néphropathie diabétique · Hormones cardiaques.
A growing interest for the understanding of the aldosterone effects in pathological fields that are not directly related to plasma volume disorders has been observed in the late years. Considered for years as a “renal hormone”, aldosterone is now recognized as a key factor in several major diseases like hypertension, LV dysfunction after myocardial infarction (MI), chronic heart failure (CHF), and renal disease. This spreading involvement of aldosterone in cardiovascular and renal pathologies comes from the recent recognition of its pro-inflammatory and fibrogenic effects, and from the discovery of extra-renal sites of synthesis of this hormone.

CHF is a major cardiovascular disease with increasing prevalence and incidence in industrialized countries. The financial burden to public health is heavy since high mortality and morbidity are associated to this disease. Moreover, this cost will increase due to aging of the population. CHF is a syndrome whose most common etiologies are MI as a result of atherosclerosis, and ventricular hypertrophy as a result of essential hypertension. The same alarming remarks (increasing incidence and financial cost) apply equally well to end-stage renal disease (ESRD). The two most important causes of ESRD are diabetic nephropathy and hypertension. A major component of CHF is the so-called neuro-hormonal activation, that has deleterious effects on myocardial function. The importance of neuro-hormonal disease is underscored by the efficacy of modern therapeutics targeted to prevent the increase or the effects of the main vasoactive hormones, i.e. angiotensin II (Ang II), aldosterone and catecholamines. Namely, clinical and experimental observations point to an essential yet incompletely defined role of aldosterone in an increasing number of multifactorial pathologies. This review will focus on the effects of aldosterone in cardiovascular and renal disease.

**Actions of aldosterone in epithelial tissues**

The physiology textbooks describe aldosterone as the main regulator of sodium reabsorption with an overall effect on body water and therefore blood volume. Aldosterone is synthesized in the zona glomerulosa of the adrenal gland, in response to Ang II, potassium and ACTH. Aldosterone-controlled sodium reabsorption takes place in kidney distal tubule and in epithelial tissues as the colon, salivary glands and skin. Sodium crosses the outer membrane of polarized cells via the amiloride-sensitive sodium channel (ENaC) and reaches then the plasma compartment via the Na+, K+-ATPase of inner membrane. The latter step thus promotes potassium excretion, and aldosterone receptor antagonists have been mainly used in clinical practice as potassium-sparing diuretics. The better known cellular action of aldosterone is to stimulate the activity then the expression of the above mentioned ionic transporters. A less known consequence of aldosterone action is the excretion of magnesium [1].

Aldosterone binds to an intracellular receptor, the mineralo-receptor (MR), present in kidney, colon, brain, heart and lung [2]. The MR is activated by aldosterone binding and is targeted to the nucleus where it binds as a homodimer to Hormone Responsive Elements (HRE) of DNA to induce the transcription of target genes. The nature of the HRE to which aldosterone binds remains poorly defined since no specific Aldosterone Responsive Elements have been identified to date. Aldosterone binds to the Glucocorticoid Responsive Elements and the intervention of still unknown tissue-specific cofactors is probably necessary to ensure either aldosterone- or glucocorticoids-specific effects. The MR belongs to a receptor family which includes glucocorticoids, androgen, estrogen and progesterone receptors. Several domains of these receptors display strong sequence similarities, which explain that the old aldosterone receptor antagonists such as spironolactone may bind other receptors and have unwanted side-effects.

This is the “classical” physiology of aldosterone but new aspects of this hormone have been discovered in the last decade, that extend its actions to the cardiovascular system and the brain (Fig 1). For example, plasma aldosterone level has been related to left ventricle (LV) mass [3]. This result is important since LV mass is a powerful index of morbidity and of mortality. In the next paragraph, we will see that a number of clinical and experimental studies have addressed different aspects of aldosterone effects, namely in pathological states.

**Aldosterone escape**

The hormonal activation of HF has been recognized as a marker of the illness and as a therapeutic target. The Renin-Angiotensin-Aldosterone System (RAAS) is activated in response to reduced cardiac output, resulting in increased levels of plasma Ang II and aldosterone. Ang-induced production of aldosterone induces sodium retention and thus
increases the cardiac preload by increase of the plasma volume. Moreover, experimental studies have evidenced that aldosterone also participates to cardiac [4, 5] and arterial [6, 7] remodeling, independently of its effect on blood pressure. The effectiveness of ACE inhibitors in HF is largely demonstrated, being mainly due to decreased Ang II synthesis. Since Ang II is the main inducer of aldosterone synthesis it was logical to think that ACE inhibition would also decrease aldosterone plasma level. This is not quite true.

Several clinical reports have shown in patients with heart failure that the plasma levels of aldosterone escape after 3-6 months of treatment with ACE inhibitor and return to high pre-treatment values [8]. This aldosterone escape during chronic ACE inhibitor treatment has also been evidenced in hypertensive patients [9], and in patients with diabetic nephropathy [10]. This phenomenon may be due to incomplete RAAS blockade, to Ang II synthesis by pathways other than the converting enzyme pathways or to a decrease in aldosterone hepatic catabolism. Whatever the cause, aldosterone escape gives a rationale for adding aldosterone antagonists to ACE inhibitors in these pathological conditions.

Aldosterone antagonists

Spironolactone has long been the main clinically available competitive inhibitor of aldosterone. In patients treated for hypertension, it has shown gestational and anti-androgenic side effects in men (impotence and gynecomasia) and premenopausal women (menstrual disturbances) [11]. These adverse effects which occur in some 7% of patients are due to the binding of spironolactone and its metabolic derivatives to progesterone and androgen receptors. Eplerenone (an epoxy derivative of spironolactone) was developed for the treatment of hypertension and congestive heart failure between 1994 and 2002 and was registered in United States as an antihypertensive drug, at daily doses of 50–100 mg [12]. Eplerenone has a 10- to 20-fold lower in vitro affinity for MR than spironolactone, but studies in humans indicate that the drug is 50% to 75% as potent as spironolactone [13]. The absence of sexual side-effects is due to its 100 to 1000-fold lower binding affinity than spironolactone for androgen and progesterone receptors. Clinical use of aldosterone inhibitors requires a tight control of potassium. This is especially important in subjects with renal insufficiency, diabetes and microalbuminuria.

Beneficial effects of aldosterone antagonists

Aldosterone antagonists in heart failure

The hormonal activation and the aldosterone escape in HF, and the discovery of aldosterone fibrogenic action in heart [4], have been determinant factors in the decision to launch the RALES (Randomized ALDactone Evaluation Study) trial. The RALES clinical study has been conducted in patients with severe heart failure (NYHA class III/IV) and has evaluated the effect of spironolactone in addition to an optimal treatment [14]. The trial has demonstrated that the addition of 26 mg/d of spironolactone to the conventional treatment of heart failure reduced mortality from all causes by 30%, and mortality of cardiovascular origin by 31%. In addition, spironolactone has a beneficial effect on cardiac function since some patients who were initially in class IV have been assigned to class III at the end of the study. The decrease in mortality observed in the RALES trial, at doses of aldosterone antagonist that had no effect on blood pressure, was unexpected and is still partly unexplained. This successful result has revivified the studies on aldosterone actions in non classical target tissues.

A decrease of cardiac fibrosis certainly played a role in the decreased morbidity and mortality of the patients enrolled in the RALES trial. Using a plasma assay of the N-terminal fragment of collagen III to estimate the cardiac fibrosis, Zannad and colleagues observed a relationship between mortality and the initial degree of cardiac fibrosis in a sub-population from RALES [15]. They also showed that spironolactone decreases cardiac fibrosis more efficiently in the patients that initially had the highest degree of cardiac fibrosis. A pro-arrhythmic role of aldosterone, which might partially depend on fibrosis, is suggested by ancient observations that would be worth re-evaluating. Indeed, the recent work of Ramires et al. described a 74% decrease of premature ventricular complexes and a 80% decrease of episodes of non-sustained ventricular tachycardia in patients with HF treated with spironolactone [16]. Preliminary results from our laboratory indicate that spironolactone given in post-MI failing rats has a prominent effect on prevention of ventricular arrhythmia by a combined action on norepinephrine content, ventricular fibrosis, ventricular excitability and heart rate variability. The exploration of heart rate variability might give pertinent information and Struthers’s team observed an improvement of this parameter in HF during spironolactone treatment, with an influence of the circadian rhythm [17]. The beneficial effects of anti-aldosterone treatment in HF is not restricted to the myocardium, since spironolactone improves endothelial dysfunction and restores the forearm response to acetylcholine in patients with HF [18]. It is thus likely that the marked reduction in sudden cardiac death observed in the RALES trial is due to a multifactorial action of spironolactone.

Aldosterone antagonists in recent post-MI

More recently, the clinical trial EPHESEUS used eplerenone at the dose of 42 mg/day in patients with acute MI
complicated by left ventricular dysfunction [19]. Patients were eligible for randomization 3–14 days after acute MI. The mean follow-up was 16 months. Again, aldosterone blockade was beneficial in patients who received optimal therapy, and significantly reduced the overall and cardiovascular mortality rate and hospitalization for cardiovascular events. Interestingly, the reduction in cardiovascular mortality was in large part due to a 21% reduction in the rate of sudden death from cardiac causes. In addition, the incidence of gynecomastia was not greater than in the placebo group. Results from similar studies in rats with LV dysfunction after extensive MI, it may be proposed that eplerenone improved LV remodeling by a complementary prevention of LV fibrosis, cardiac hypertrophy, and molecular alterations [20].

Aldosterone antagonists in hypertension

Eplerenone is approved for hypertension in the United States, with primary aldosteronism (PHA) as a specific target. Presence of PHA in patients with essential hypertension has been previously underestimated, and it is likely that it may represent 10% or more [21]. Patients with primary aldosteronism, who usually have very low circulating Ang II levels, have a higher incidence of left ventricular hypertrophy [3], albuminuria [22], and stroke [23] than do patients with essential hypertension. A dose-dependent antihypertensive effect of eplerenone has been demonstrated in several studies [13]. Despite efficient in lowering blood pressure, it seems that a key feature of anti-aldosterone therapy in hypertension is related to prevention of organ damage. In aged patients with systolic hypertension, eplerenone was as effective as amlopidine to lower blood pressure and improve vascular compliance, but was more effective to reduce microalbuminuria [24]. Sato and colleagues observed that both enalapril and spironolactone decreased blood pressure to the same extent in essential hypertensives, but the regression of left ventricular hypertrophy was significantly greater with enalapril plus spironolactone than with enalapril alone. As in the RALES sub-study [15], they found that the decrease of the procollagen type III amino-terminal peptide was greater in patients with higher levels at baseline [25]. In essential hypertensives with left ventricular (LV) diastolic dysfunction, Grandi et al. found that patients treated with canrenone (a spironolactone derivative) showed a significantly greater improvement of LV diastolic function than patients treated with ACE inhibitors alone [26]. Here also, this improvement, not accounted for by changes in blood pressure and left ventricular mass, may be therefore ascribed to a direct action of the drug on the myocardium. At last, the 4E-LVH study conducted in hypertensive patients with left ventricular hypertrophy showed that the eplerenone/enalapril combination was more effective in reducing urinary albumin excretion than enalapril or eplerenone alone, indicating that the renoprotective effects of aldosterone antagonists and ACE inhibitors were additive [27].

Aldosterone antagonists in renal disease

Although much evidence shows that angiotensin II mediates progressive renal disease, recent evidence also implicates aldosterone as an important pathogenetic factor in progressive renal disease [28]. Indeed, several clinical investigations identified increased aldosterone levels in renal insufficiency. Diabetic nephropathy has become the leading cause of end-stage renal disease in many countries, and early identification and subsequent renoprotective treatment are thus of utmost importance. In this context, it has been established that ACE inhibitors are of specific benefit not only in reducing proteinuria but in retarding the progression of diabetic nephropathy. Recently, however, it has been reported that although the use of ACE inhibitors may be beneficial for patients with nondiabetic renal diseases, approximately half of these patients were improved only at the beginning of treatment and subsequently escaped from antiproteinuric effects of an ACE inhibitor [29]. In hypertensive patients with type 2 diabetes and microalbuminuria, Epstein et al. observed that the eplerenone-treated group demonstrated a 62% reduction in the urinary albumin excretion rate during the 6-mo period, compared with a 45% reduction in the enalapril group and a 74% reduction in the combination group [30]. This significant reduction in proteinuria in the eplerenone treated group was independent of the change in BP from baseline values. Sato et al. [10] have shown that aldosterone escape is observed in 40% of patients with type 2 diabetes with early nephropathy despite the use of ACE inhibitors. In patients with escape, spironolactone decreased urinary albumin excretion and left ventricular mass index without blood pressure change. This suggests the possibility that aldosterone blockade may represent optimal therapy for patients with early diabetic nephropathy who show aldosterone escape during ACE inhibitor treatment and who no longer show maximal antiproteinuric effects of ACE inhibition.

Effects of aldosterone in cardiovascular and renal system

It is thus clear that anti-aldosterone treatment has beneficial effects in several pathologies, beyond the lowering in blood pressure. Experimental studies of aldosterone effects on cardiovascular target organs may help to understand the beneficial consequences of the treatment by spironolactone or eplerenone.

Cardiac fibrosis

One of the best documented effects of aldosterone is the induction of a significant cardiac fibrosis with detrimental consequences on the cardiac pump and an arrhythmogenic effect. Experimentally obtained in rat by an aldosterone
and salt overload, fibrosis appears in both ventricles whereas ANP increase and myocyte hypertrophy are restricted to the left ventricle, strengthening the hypothesis that the fibrogenic response is independent of hemodynamic factors [4, 5]. To further confirm this independent effect of aldosterone, spironolactone at 20 mkd prevents fibrosis but neither the hypertension nor the left ventricle hypertrophy associated with the treatment change [4]. The steps that lead to fibrosis, particularly the role of sodium, are not well understood. Ang II may be a key factor since the cardiac [31] and vascular [32] density of the Ang II AT1 receptor is increased in aldosterone treated rats.

**Vascular injury**

Experimental animal data support a role for aldosterone in mediating cardiovascular injury in the kidney and brain. In the stroke-prone spontaneously hypertensive rat (SHRSP), a genetic model of spontaneous hypertension, administration of spironolactone greatly attenuated renal and cerebral vascular damage [33]. Likewise, in the remnant kidney hypertensive rat, administration of aldosterone reversed the renal protection given by blockade of the RAAS with combined ACE inhibition/ AT1 receptor antagonist treatment [34]. Thus, in the kidney and brain, aldosterone may have deleterious effects on the vasculature that may be independent of other components of the RAAS. Recently, it was proposed that the profibrotic effects of aldosterone in the heart are a consequence of myocardial ischemic and necrotic alterations rather than a direct effect of aldosterone on extracellular matrix deposition. This hypothesis was suggested after the observation that administration of eplerenone, as well as adrenalectomy, attenuated vascular lesions and myocardial necrosis in a model of ANG II-induced hypertension [35]. Two laboratories have observed the induction of a peri-coronary inflammatory phenotype in the hearts of aldosterone-salt treated rats [36, 37]. Since upregulation of markers of inflammation or inflammatory cells, Cox-2 and MCP-1, is observed as soon after aldosterone challenge, proliferation of inflammatory cells around the coronary arteries may be one of the early events that ultimately result in cardiac fibrosis [38]. The causative role of oxidative stress in this aldosterone-mediated vascular alterations is strongly suggested by the fact that spironolactone or antioxidants independently prevent these changes in either coronary [37] or peripheral [39] vessels. Similarly, eplerenone reduced the increased vascular superoxide formation observed in aortic rings of rats with CHF after MI [40]. Young and colleagues have shown that vascular smooth muscle cells, which express MR and 11-beta-HSD1/2 with 11-beta-HSD1 showing uncharacteristic oxidase activity, are a target for mineralocorticoids [41]. They observed that 11-deoxy corticosterone or carbeneoxolone can both induce the expression of inflammation markers in rat heart, suggesting that local glucocorticoid excess may mimic mineralocorticoid excess, and play a direct etiologic role in coronary vascular inflammatory responses under circumstances of a high salt intake.

**Early steps**

Together, these results show that aldosterone induces early vascular damages (that are part of the vascular deterioration observed in human’s heart failure) that are probably one of the factors that induce fibroblasts activation before the observed fibrogenic remodeling (Fig 2). One of the primary steps leading to the observed inflammatory phenotype may involve ionic changes. Indeed, non-epithelial cells are not polarized which means that aldosterone does not induce transcellular ionic transport there (if we hypothesize that aldosterone controls ionic movements in cardiac cells as it does in kidney cells). Thus, the major consequence of aldosterone action in non-epithelial cells is likely a modification of their intracellular ionic composition. In this context, Weber and colleagues reported an early decrease of intracellular magnesium and calcium concentrations in circulating monocytes and lymphocytes of rats treated with aldosterone-salt [42]. Markers of oxidative and nitrosative stress in plasma (alpha-1-antiproteinase activity) and cardiac tissue (gp91phox subunit of NADPH oxidase and 3-nitrotyrosine) were found increased in these animals. Despite ionic changes in cardiac cells were not shown in this work for technical reasons, is is suggested that all these events, from the ionic disturbances and oxidative stress to

**Figure 2**

Tentative scheme of initial events triggered by aldosterone increase in heart failure. This scheme is a combination of results from several works, namely Gerling et al., 2003; Nicoletti et al., 1999; Silvestre et al., 1999.
coronary vascular lesions and perivascular fibrosis, may occur in the tissue.

**Synthesis of aldosterone in heart**

The mitochondrial P-450 aldosterone-synthase (AS) catalyzes the synthesis of aldosterone from 11-deoxycorticosterone in the adrenal cortex. However, extra-adrenal sites of aldosterone production have been identified in the heart [43] and vessels [44] of rodents, as well as in the pulmonary artery of human subjects [44]. The rat heart expresses two key factors of aldosterone synthesis, the Steroidogenic Acute Regulatory (StAR) protein which plays a pivotal role in intramitochondrial cholesterol transfer, and AS [43, 45]. The AS mRNA is 500-1000 fold lower in heart than in the adrenal gland, which would correspond to a low level of cardiac aldosterone synthesis and could be considered insignificant. However, it should be realized that the hormone produced in cardiac tissue will act in conditions very different from those for the circulating hormones, i.e. on a very limited volume and with a short time response. Thus, it is possible that instantaneous high concentrations of aldosterone may be reached locally despite a low rate of production. Interestingly, this local synthesis is stimulated after MI in parallel with the local synthesis of Ang II [46]. The ventricular fibrosis observed in the non infarcted part of the left ventricle is totally prevented by losartan, and partly by spironolactone. Since the circulating level of these hormones is normal, cardiac fibrosis has been linked to the local production of these two hormones. The aldosterone concentration, already 15 times higher in normal rat heart than in plasma, rises by another factor of 3 in the noninfarcted part of left ventricle. A tissue renin-angiotensin-aldosterone system thus exists in heart, and depending on the local conditions, which may be quite different from those estimated from the plasma assays, its role in cardiovascular pathology may be important (review in [47]). Study of this local system is complicated by its low level of expression and also by the difficulty of distinguishing the effects of aldosterone derived from the tissue from those derived from circulating hormone. Transgenic mice have been generated in our laboratory that overexpress AS in the heart when the AS gene is targeted via the alpha-myosin heavy chain promoter. Preliminary results indicate that increased cardiac aldosterone production induces no significant change of cardiac function but does cause major coronary dysfunction. This may have harmful consequences on coronary adaptation to increased flow demand.

In human heart failure, cardiac aldosterone production is increased and there is a relationship between this increase and the level of ventricular dysfunction [48]. Very recently, three laboratories have described an increased AS gene expression, with a relationship to cardiac fibrosis and left ventricle dysfunction, in fresh ventricular biopsies obtained from patients with HF (review in [49]) or with hypertrophic cardiomyopathy [50]. In addition, aldosterone concentration was increased in the heart whereas it was unchanged in the plasma of patients with hypertrophic cardiomyopathy [50]. If the cellular types of synthesis are still undetermined, recent work detailed above suggest that vascular cells may be one of the primary targets of this aldosterone generated “from the inside”.

**Unsolved questions**

There are a number of unsolved questions regarding the mechanisms of aldosterone action in heart. Our current knowledge of the corticosteroid receptors system raises namely the question of the binding of aldosterone to its receptor in heart. In epithelial cells glucocorticoids (that are 100 to 1000 fold higher than aldosterone in plasma, and may bind the MR) are inactivated by the type 2 11-beta-hydroxysteroid-dehydrogenase. This enzyme has been evidenced in the human and rodent heart but its enzymatic activity is too low to protect the cardiac MR from glucocorticoids [2]. Thus, other mechanisms are required to explain the aldosterone specific binding [2], or one must admit that the cardiac MR is predominantly occupied by glucocorticoids [51]. Recently, the cardiac specific overexpression of 11HSD2 has confirmed the deleterious consequences of inappropriate activation of cardiomyocyte MR by aldosterone. The spontaneous cardiac hypertrophy, fibrosis and heart failure that developed in these mice was ameliorated by eplerenone [52]. The authors conclude that, since cardiac MR is occupied by glucocorticoids in normal conditions, their work reveals a tonic inhibitory role of glucocorticoids in preventing such outcomes under physiological conditions. Several questions still remain as regards the mechanisms since the partial inactivation of the cardiac MR by an inducible anti-MR antisens RNA in mice causes a syndrome of congestive HF associated with a major cardiac fibrosis [53]. This observation suggests that the action of aldosterone in heart may involve an equilibrium between MR and GR, and that some of the effects of aldosterone may be mediated by other receptors than the MR, for example the GR.

**Conclusion**

It is now recognized that anti-aldosterone treatment has beneficial effects in several pathologies, including hypertension, LV dysfunction after MI, chronic heart failure, and renal disease. These effects are observed beyond the lowering in blood pressure, pointing to protection against organ damage in cardiovascular system. Experimental studies of aldosterone effects in cardiovascular target organs allow now to partly understand the cellular and sub-cellular effects of aldosterone. These advances will be useful for optimization of the treatment of these increasingly occurring pathologies.

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