ORIGINS OF RENAL DISEASES

The story of spironolactones from 1957 to now: from sodium balance to inflammation

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Abstract
After the discovery of aldosterone (1953), many synthetic steroids were tested for their ability to block the sodium retaining and potassium excreting effect of synthetic mineralocorticoids in adrenalectomized rats. In the same years Kagawa discovered that 17-spirolactone steroids were effective to block mineralocorticoid effects, but when used alone they did not produce any effect in adrenalectomized rats.

After the description of the first case of primary aldosteronism (1955), spironolactone (SP) was considered the main treatment before surgery to control blood pressure and kaliemia and for long-term treatment in patients with bilateral adrenal hyperplasia.

SP was further used for various clinical situations, such as liver cirrhosis, idiopathic oedema, nephrosis and congestive heart failure. SP also shows an antiandrogen action, effective in polycystic ovary syndrome.

In 1985 we demonstrated that human mononuclear leukocytes (MNL) possess mineralocorticoid receptors (MR) and lately we demonstrated that coincubation of MNL with canrenone blocked aldosterone mediated inflammatory, reducing the expression of PAI-1 and p22phox. It is well known that MNL and macrophages are mainly involved in vascular inflammation and atherosclerosis and we have hypothesized that the tissue invasion of MNL brings MR in the site of inflammation starting the process.

Recently, aldosterone has been associated with the promotion of many organ-specific autoimmune diseases, inducing Th17 polarization of CD4+ T cells and suggesting new possible therapeutic targets for antimineralocorticoid drugs.

In conclusion, considering all the benefits of MR-antagonists, their use should be reconsidered not only for the treatment but also for the prevention of many clinical situations.

Key words: aldosterone, canrenone, hypertension, inflammation, mineralocorticoid receptor, mineralocorticoids, spironolactone
potent anti-mineralocorticoid effect; this compound was called aldactone. In the same period, Kagawa and coll. demonstrated that SP was able to block the sodium-retaining and kaliuretic-excreting activity of aldosterone and of other mineralocorticoid active compounds like DOC, cortisol and 9-alpha-fluorocortisol. On the other hand, when used alone these compounds did not produce any effect in adrenalectomized rats [4][5], while in patients with Addison disease treated with desoxycorticosterone acetate (DOCA) they were able to reverse the effect of DOCA on sodium and potassium excretion.

In 1955 Jerome Conn described the first case of primary aldosteronism, characterized by an aldosterone-producing adrenal adenoma [6]. The unilateral adrenalectomy resolved the clinical symptoms of the syndrome and SP was considered the main treatment of these patients both before surgery to normalize blood pressure and serum potassium both for long-term treatment in patients with bilateral adrenal hyperplasia with or without a marked nodular hyperplasia (idiopathic hyperaldosteronism).

The antagonism of SP is not only evident in renal sodium transport, but also in the ionic equilibrium of other tissues, for example in red blood cells [7][8], intestine, salivary and sudoripary glands. SP was also used for various clinical situations, as liver cirrhosis, idiopathic oedema [9], ascites, nephrosis, congestive heart failure and various hypertensive vascular diseases; it was also particularly indicated in the hypokalemic state caused by diuretics, in nephritic syndrome [10] and in the treatment of cardiac oedema of patients refractory to the usual diuretics. The only contraindications to SP therapy is in case of renal insufficiency, because of a possible worsening of hyperkalemia, and when SP is given in association with thiazides, because hyperkalemia tends not to improve [11].

An important question raised in the subsequent years is whether SP can affect directly the secretion of aldosterone at the level of adrenal glomerulosa. In 1963 Jancigan demonstrated that patients treated with SP do have cytoplasmic inclusions in the adrenal called "spironolactone bodies" [12]. In the same period, we reported that administration of SP in patients with primary aldosteronism reduces the urinary aldosterone in the first period of treatment when renin is still suppressed, while later renin and aldosterone increase due to the diuretic effect of SP [13].

Searle and other companies later tested different analogues of SP and the more interesting derivatives for clinical application were potassium canrenoate, canrenone and more recently eplerenone. SP do also have an important antiandrogen effect, which is lower in potassium canrenoate and canrenone and absent in eplerenone [14][15].

This different actions increase the use of SP also as an antiandrogen, for example in polycystic ovary syndrome [16][17], while potassium canrenoate and canrenone are mainly used as antiminerocorticoid drugs.

**Aldosterone, spironolactones and inflammation**

In the last decades, many studies revaluated the role of aldosterone in the pathogenesis of inflammation. This process is preceded by peripheral blood mononuclear leukocytes (MNL) invasion, but it is still not clear if MNL are activated before tissue invasion or they are attracted in the inflammatory site by local factors.

In 1985 we demonstrated that human lymphomonocytes possess the mineralocorticoid receptor (MR), where aldosterone regulates intracellular electrolytes and volume [18][19][20]. Subsequently we demonstrated that coinubation of MNL with canrenone blocked the inflammatory effect of aldosterone, reducing the MNL expression of two markers of oxidative stress, PAI-1 and p22phox [21].

In the late 1980th Pitt and coll. found that SP and eplerenone are potent anti-inflammatory drugs, blocking the inflammatory effect of aldosterone in non-epithelial cells, such as vascular smooth muscle, renal and myocardial cells. These studies supported the addition of anti-mineralocorticoid drugs to the conventional treatment of many pathological conditions characterized by secondary aldosteronism, reducing the prevalence of a relapse of heart failure and of cardio-cerebrovascular accidents [22](full text) [23].

Other studies suggested a role of aldosterone in the pathogenesis of atherosclerosis and of anti-mineralocorticoid drugs in blocking this process. In particular, eplerenone induces reduction of oxidative stress and arteriosclerosis progression in apolipoproteins E-deficient mice and in monkey fed with a high cholesterol diet but with normal aldosterone plasma levels [24][25](full text). It is well known that MNL and macrophages are mainly involved in vascular inflammation and atherosclerosis. Based on these studies, we suggested that a possible link between aldosterone, inflammation and atherosclerosis could derive by the increased cholesterol concentration at the level of the arterial wall, which induces an inflammatory process, attracting MNL with the MR available for binding of aldosterone, that may act as a pro-inflammatory factor even in tissue which do not have MR [26](full text).

Many authors are exploring the use of SP as anti-inflammatory drug, being effective for example in the treatment of ocular chorioretinopathy and of arthrits [27][28](full text).

More recently we also found that aldosterone can induce remarkable membrane alterations of erythrocytes, leading to their premature removal from circulation. This effect is blocked by coinubation with canrenone, suggesting that also the so-called non-genomic effects of aldosterone could be mediated by the MR [29].

Finally, the relationship between aldosterone and autoimmune disorders is a new area of investigatation. Recently Herrada et al. demonstrated that aldosterone can directly increase the capacity of
dendritic cells to activate CD8+ T cells and induce Th17 polarization of CD4+ T cells, which have been associated with the promotion of many organ-specific autoimmune diseases, such as rheumatoid arthritis and autoimmune thyroiditis [30] (full text). In particular, a recent article reported a case of a female affected by primary aldosteronism and autoimmune thyroiditis, to whom surgical removal of an aldosterone-producing adrenal adenoma improved thyroid function and decreased thyroid autoimmunity [31]. These data suggest that SP could ameliorate the evolution of some autoimmune diseases, proposing new therapeutic targets for antimineralcorticoid drugs.

**Perspective**

Actually the normal concentration of aldosterone is not related to the crude value but rather to the aldosterone/plasma renin activity ratio; however, the administration of MR- antagonists is useful to prevent cardiovascular risk even in patients with normal aldosterone values, pointing out on the importance of these drugs not only for hyperaldosteronism but also for essential hypertension.

Recently, the guidelines of the European Society of Hypertension (ESH) has recommended the use of MR-antagonist only for the treatment of patients with hypertension resistant to the conventional polytherapy. In our experience, we think that some cases of hypertension were resistant because MR were not still blocked. Considering all the benefits of MR-antagonists, their use should be reconsidered not only for the treatment but also for the prevention of many clinical situations [32].

**References**


