Aldosterone antagonism: new ideas, new drugs

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Abstract

In the last few years our ideas about the physiological and pathological roles of aldosterone have changed enormously. It is now widely recognised that this hormone not only plays a crucial role in normal salt and water regulation, and its abnormalities in congestive heart failure and some types of hypertension, but also has other effects. These may include the promotion of cardiac and vascular inflammation and fibrosis and increased likelihood of arrhythmias. These perspectives coincide with a revived interest in aldosterone antagonists, particularly since the RALES trial showing the benefits of spironolactone in patients with congestive heart failure. This long-established drug does unfortunately have serious adverse effects, notably gynaecomastia and menstrual abnormalities. New drugs, such as eplerenone, are being developed which are more selective for the aldosterone receptor and have less interaction with receptors for other steroid hormones. Early studies indicate that this drug may have comparable efficacy to spironolactone in patients with hypertension and heart failure, while adverse effects appear to be less frequent and severe. The development of such compounds will encourage greater emphasis on aldosterone antagonism in cardiovascular drug therapy.

Key words: aldosterone, spironolactone, aldosterone antagonists, renin angiotensin system, heart failure.

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Introduction

If we still lived in salt water we would not need aldosterone, however most mammals – like ourselves – do not. Aldosterone has been recognised for many years as a key hormonal regulator of extracellular volume and electrolyte composition and, as a consequence, also of blood pressure.[1] It is produced in the zona glomerulosa of the adrenal cortex and is the final hormonal product of the renin-angiotensin system. Its release is stimulated by angiotensin II and by increases in plasma potassium levels but *not* by ACTH.

The kidney has been regarded as the primary target for the

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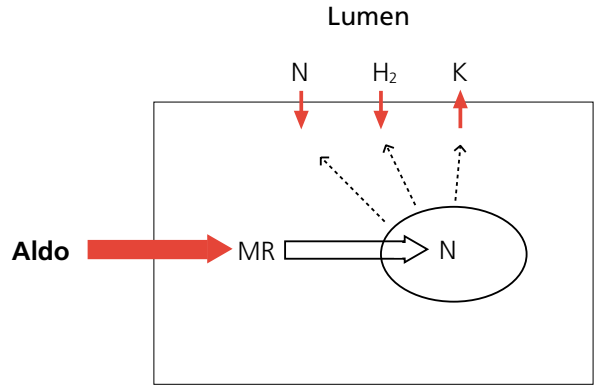
Figure 1. Simplified scheme of action of aldosterone (aldo) in collecting duct and distal tubule of kidney. Aldosterone binds to the cytoplasmic mineralocorticoid receptor (MR) and the complex is translocated to the nucleus (N) where it induces transcription of genes involved in membrane channel regulation, among other functions



homeostatic action of aldosterone – figure 1 summarises the 'classical' actions of the hormone on the epithelium of the distal tubule of the nephron. It has long been recognised that these receptors are also present in epithelia of other tissues, such as the colon and salivary glands. These receptors are members of the huge superfamily of nuclear receptors mediating many of the effects of steroids, thyroid hormones and retinoids by genomic effects, that is, requiring gene transcription and new protein synthesis.

In the last few years our understanding of aldosterone receptors has been greatly extended in two directions:

- It is now clear that genomic aldosterone receptors are also found in non-epithelial tissues, particularly the heart and the brain. Additionally it has been suggested that these tissues can also synthesise aldosterone, as can some blood vessels.[2]
- Some of the effects of aldosterone are too fast to be genomic and are *not* blocked by the aldosterone receptor antagonist spironolactone or by any other drug at present in clinical use. This receptor has not been fully characterised but it activates calcium mobilisation, for example in vascular smooth muscle, as well as rapid changes in sodium channels.[1,2]

The remainder of this review will focus mainly on some of the new concepts of aldosterone-related pathophysiology in the cardiovascular and renal systems, in particular the relevance of old and new aldosterone antagonists.

Hypertension and heart failure: established associations of excess aldosterone

Primary hyperaldosteronism

Primary hyperaldosteronism (Conn's syndrome) has been known for 40 years as one of the relatively common causes of secondary hypertension. Its true frequency is still disputed, but may be about 10–15% of the hypertensive population.[3] The original description of the disease implicated adrenal adenomas but hyperplasia can also produce the characteristic picture of a high aldosterone: renin ratio, with excess of one and relative suppression of the other. Hypokalaemia is usual but far from inevitable. Although it was believed that hypertension in this syndrome was relatively mild and easily managed, it is now clear that it is often severe, even leading to malignant hypertension. It is also difficult to manage without (and sometimes even with) the use of spironolactone; this drug will be discussed later.

The process by which hypertension occurs in this situation is far from clear. It is interesting that direct injection of aldosterone into the cerebral ventricles will produce hypertension much more readily than infusing large doses of the hormone into the systemic circulation. It is notable that oedema does not occur in these patients in the absence of other pathology. It is also clear that some patients with hyperaldosteronism, particularly when this is one of the rare familial forms, are actually normotensive but still have evidence of cardiac and vascular damage. The pivotal role of aldosterone in blood pressure regulation is emphasised by the fact that most of the single gene causes of hypertension involve this hormone in some respect.

Table 1. Potentially damaging effects of aldosterone on the cardiovascular system and the kidney

- Sodium and water retention
- Hypokalaemia
- Hypomagnesaemia
- Cardiac hypertrophy and fibrosis
- Endothelial dysfunction
- Vascular inflammation and fibrosis
- Potentiation of sympathetic nervous system/arrhythmogenesis
- Impaired fibrinolysis
- Nephrosclerosis

Table 2. Mechanisms by which aldosterone may promote fibrosis

- Generation of reactive oxygen species
- Upregulation of angiotensin II receptors
- Stimulation of transforming growth factor β synthesis
- Increased sodium influx into vascular wall
- Potentiation of effects of noradrenaline

Secondary hyperaldosteronism

Secondary hyperaldosteronism is probably more familiar in practice to the majority of clinicians. It includes patients with hypertension due to renovascular disease, patients in the malignant phase of hypertension regardless of the underlying cause, hepatic cirrhosis and, most commonly, congestive heart failure.[4] In all these circumstances there is activation of the renin-angiotensin-aldosterone system and levels of circulating aldosterone may approach or even exceed those in Conn's syndrome. There is sodium retention and expansion of extravascular and circulating volumes. In the last two conditions oedema is usually found but hypertension is not, though the reasons for this divergence are poorly understood.

Spironolactone was long a cornerstone of the management of ascites complicating hepatic cirrhosis but its use in heart failure was more controversial until relatively recently, although aldosterone was recognised as a significant contributor to the clinical aspects of the disease. The understanding of this contribution has also undergone major expansion in the last decade.

New aspects of aldosterone pathophysiology

Table 1 describes pathological processes in the cardiovascular and renal systems associated with aldosterone excess,[5-7] with some of the hormone generated within tissues other than the kidney. These are discussed in detail in the references cited, but it is important to draw attention to two aspects. Firstly, that aldosterone appears to be a major promoter of hypertrophy and especially of fibrosis in the heart, peripheral vessels and the kidney.[8,9] Possible underlying mechanisms are summarised in table 2. Experimental evidence strongly supports the protective effect

of aldosterone antagonism. Secondly, aldosterone excess is arrhythmogenic, at least in part, because the hormone increases effective noradrenaline concentration and hence sympathetic activation by blocking uptake. In addition, cardiac hypertrophy and fibrosis is also associated with increased risk of arrhythmia. Here too spironolactone appears to be beneficial.

Spironolactone

Spironolactone was synthesised 30 years ago and classified as a potassium-sparing diuretic before its relationship to aldosterone was fully established. It was widely used as an antihypertensive drug in patients without evidence of hyperaldosteronism and appeared to have efficacy at least comparable to the thiazides, with a very gradual onset of hypotensive action.[10] The latter have very largely supplanted it in essential hypertension. At the same time, the introduction of ACE inhibitors for the treatment of congestive heart failure was associated with the assumption that these drugs would effectively suppress aldosterone secretion by their 'upstream' effect on angiotensin II generation. As a result, the use of spironolactone in such patients declined. However, evidence accumulated that the high levels of aldosterone were only incompletely suppressed and that 'escape' frequently occurred after initial efficacy. In fact this was noted in some of the landmark ACE inhibitor trials.[11,12] There was therefore an increasing incentive to test the usefulness of spironolactone in patients already optimally dosed with ACE inhibitors.

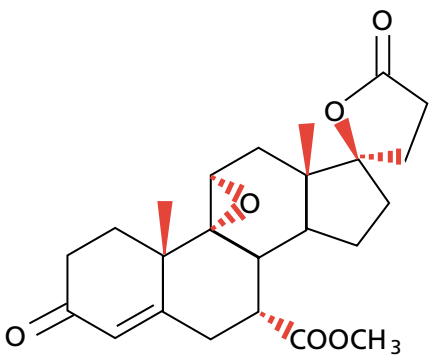
The Randomised Aldactone Evaluation Study (RALES) did exactly this,[13] adding spironolactone 25 mg daily to half the patients in a placebo-controlled trial involving over 1,600 subjects in New York Heart Association (NYHA) classes II to IV. After two years the study was terminated because there was a clear reduction in deaths (by 30%) and in hospitalisations (35%), with some improvement in NYHA class. Serious hyperkalaemia, an obvious concern when adding spironolactone to ACE inhibition, occurred in only 2% of cases, very similar to the placebo group.

Naturally, this encouraged many more clinicians to use spironolactone in heart failure and reinforced the views of those already doing so. However, the drug is not ideal. About 10% of male patients in the RALES trial suffered gynaecomastia and this is in keeping with general clinical experience. The drug has long been known to have antiandrogenic properties (occasionally exploited in the treatment of hirsutism) and is also progestagenic and may cause menstrual abnormalities. So, despite the proven usefulness of spironolactone, a better aldosterone antagonist is desirable.

Eplerenone

Eplerenone (figure 2) has been developed to fill this role (reference 14; see also website cited). It may be marketed in the USA in the next year, though probably not in Europe. It has a 20-fold lower receptor affinity for the classical aldosterone receptor *in vitro* than does spironolactone, but the effective dose in oral dosing is similar or lower. This may be due to the more extensive protein binding of spironolactone. At the same time, affinities of eplerenone for the androgen and progestagen receptors is about

Figure 2. The chemical structure of the selective aldosterone receptor antagonist eplerenone



SC-66110
(Eplerenone)

Table 3. Experimental effects of eplerenone on aldosterone-associated cardiovascular and renal dysfunction

- Blockade *in vivo* of renal effects of hormone
- Reduced vascular inflammation and fibrosis
- Reduced post-MI fibrosis (but not healing)
- Reduced myocardial fibrosis in experimental models of hypertension
- Reduced renal damage in experimental models of hypertension

100-fold less than that of spironolactone. On this basis eplerenone has been called a Selective Aldosterone Receptor Antagonist (SARA). The evidence for the efficacy of eplerenone in physiological and pathophysiological antagonism of aldosterone is summarised in table 3. The pharmacokinetics of the drug are straightforward with rapid absorption and elimination (half life ~4 hours), mainly by metabolism involving the cytochrome P450 3A4 isoform, the most common type involved in drug metabolism in humans. The peak-trough ratio is described as suitable for once-daily dosage, although details of this are not available. No unexpected toxicity emerged during preclinical studies.

Clinical studies

Published clinical information on this drug is rather limited and none has so far appeared in full papers. A phase II dose-ranging study in mild to moderate hypertensives compared eplerenone 50, 100 or 400 mg daily (as a single dose) with spironolactone 50 mg bd and placebo, over a 12-week period. The highest dose of eplerenone reduced clinic systolic blood pressure/diastolic by 15/8.9 mmHg as compared to 16.7/9.5 mmHg for spironolactone: the figures are corrected for placebo. Comparable reductions were described with ambulatory blood pressure monitor-

Table 4. Comparative effects of eplerenone and losartan in black and white patients with moderate hypertension

	Systolic blood pressure		Diastolic blood pressure	
	Eplerenone	Losartan	Eplerenone	Losartan
Black	-9.8	-1.6	-5.4	-1.2
White	-9.1	- 5.3	-4.7	-2.2

Figures are mmHg corrected for placebo

Doses: eplerenone 200 mg daily; losartan 100 mg daily

ing. Another study compared eplerenone 50–200 mg daily with losartan 100 mg daily and placebo. This study was specifically designed to compare responses in black and white patients and its outcome is summarised in table 4. Losartan has poor efficacy in black hypertensives, even compared to placebo and certainly as compared to eplerenone. The two drugs have similar efficacy in whites. Finally, a complex study involving the addition of eplerenone 50–100 mg daily in patients whose blood pressure is inadequately controlled on an ACE inhibitor or angiotensin receptor blocker (ARB) on their own shows an interesting additional effect on systolic but not diastolic blood pressure. Nothing is yet available on the uses of eplerenone in hypertension associated with primary hyperaldosteronism.

There is limited accessible information on the uses of eplerenone in heart failure. A phase II dose-ranging study of eplerenone 25–100 mg daily compared to spironolactone 25 mg or placebo in NYHA class II to IV patients on ACE inhibitors showed similar reduction in brain natriuretic peptide, as a surrogate, but the trial was not powered or designed to assess clinical efficacy.

In this study there were more patients with hyperkalaemia (K^+ 6 mmol/L or more in the eplerenone group than the spironolactone group (12 *vs.* 8.7%). In the hypertension trials there is a much lower incidence of hyperkalaemia, about 1–2%, possibly reflecting impaired renal function in patients with heart failure. It is important to note that gynaecomastia has not so far been described in association with eplerenone and neither have menstrual disturbances.

A very recent study presented at the American College of Cardiology meeting in Atlanta, USA, earlier this year, examined eplerenone 200 mg daily, enalapril 40 mg and a combination of eplerenone 200 mg with enalapril 10 mg daily in about 200 hypertensive patients with left ventricular hypertrophy (the 4E study). The authors concluded that the efficacy of the two drugs was similar in reducing both blood pressure and left ventricular hypertrophy, but patients on enalapril needed more add-on antihypertensive medication. The combination of the two drugs produced greater falls in blood pressure than either alone but the effects were not additive (e.g. systolic blood pressure was reduced by 23 mmHg by eplerenone, 25 mmHg by enalapril and 29 mmHg by the combination). The picture was similar for reduction in left ventricular mass (14.5, 19.7 and 27.2% respectively).

Key messages

- High levels of circulating aldosterone can cause not only sodium retention and hypertension but also direct damage to the heart and blood vessels
- Spironolactone, an aldosterone receptor blocker, has been shown to have significant benefit in heart failure but adverse effects are frequent
- More selective receptor antagonists, such as eplerenone, appear to have similar efficacy to spironolactone but with fewer side effects
- Such drugs should encourage the more widespread use of aldosterone antagonists in cardiovascular disease

Ongoing trials with eplerenone in hypertension include a comparison with amlodipine; a comparison with enalapril alone and with a combination of the two drugs in hypertensive patients with left ventricular hypertrophy; and a similar study in type 2 diabetes – it is not clear whether these patients will all have raised blood pressure. Perhaps the most ambitious trial, however, is EPHESUS, the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (with a very pleasing neo-classical logo!). It is already in progress and will compare eplerenone 25–50 mg daily with placebo in over 6,000 patients who have survived acute myocardial infarction but have systolic left ventricular dysfunction. Patients are randomised within two weeks of the acute event and the trial will end when 1,012 deaths have occurred. Primary end points are all-cause mortality, cardiovascular mortality and hospitalisation. Presentation of the results is expected in spring of 2003.

Summary and prospects

There has been a striking revival of interest in the basic biology of aldosterone and its clinical implications; we now appreciate that excess aldosterone can cause far more problems than we had suspected. The usefulness of aldosterone antagonists in heart failure is not in doubt and there is more interest in a possible role in essential hypertension as well as in Conn's syndrome. It may be that they can again – to some extent – challenge the thiazide diuretics in this respect, especially since they avoid the problem of hypokalaemia. Eplerenone, a new SARA, appears to avoid the unwanted and unpleasant hormonal effects of spironolactone and its efficacy looks promising: however, this needs to be fully confirmed especially in heart failure. In any case, fundamental and clinical research in this area seems certain to grow, and other drugs in this class are likely to emerge, with perhaps greater potency and efficacy combined with high selectivity.

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See also:

New insights into the role of aldosterone in cardiorenal disease and the clinical implications (2002) on http://www.medscape.com/viewprogram/1004_pnt