Aldosterone, a vasculotoxic agent—novel functions for an old hormone

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Keywords: aldosterone; hyperaldosteronism; hypertension; inflammation; proteinuria

Aldosterone and blood pressure—beyond Conn syndrome

In 1955, the syndrome of primary aldosteronism was described by and subsequently named after J. W. Conn [1]. It was defined as high aldosterone concentrations in the presence of adrenal adenoma or bilateral hyperplasia. Recently, the definition of the syndrome has been expanded and the—claimed or real—frequency has risen sharply [2]. An animated discussion is going on whether we are really dealing with a true rise in the frequency of primary aldosteronism as originally defined.

New data allow a more sophisticated and broader interpretation of the role of aldosterone. In the Framingham offspring study, it had been documented that the frequency of a rise in blood pressure and the incidence of hypertension increase progressively from the first to the fourth quartile of serum aldosterone concentrations [3]. This led recently to the comment ‘whether primary aldosteronism is as widespread as some believe may not be as relevant as whether the commonly prevailing level of aldosterone is too high for the amount of sodium we consume’ [4].

Aldosterone plays a more general role in the genesis of hypertension, it was also stated that ‘aldosterone . . . contributes to the development of hypertension . . . more than even the most generous estimates for the prevalence of primary hyperaldosteronism’ [4]. This interpretation finds support in some recent experimental data. Makhanova [5] created salt-sensitive blood pressure in mice by increasing the expression of aldosterone synthase by manipulating the untranslated regions of aldosterone synthase gene in mice, raising aldosterone synthase mRNA by a factor of 1.5. On low salt, such mice had normal blood pressure but less activation of RAS (renin–angiotensin system) than wild type. On high salt, however, blood pressure was higher by 10 mmHg, accompanied by hypokalaemia and increased expression of collecting duct sodium channel (ENaC). Along these lines, a study in humans [6] found a correlation between an aldosterone synthase polymorphism (344T/C) and aldosterone excretion as well as hypertension; this observation has recently been confirmed by one study [7] but not by another one [8]. It is likely that the blood pressure-raising effect of aldosterone is not only the result of natriuresis and sodium balance; in anuric dialysis patients, 50 mg spironolactone lowered systolic blood pressure by 11 mmHg, remarkably without a change in serum potassium and presumably as a result of a direct vasoconstrictive effect [9].

Activation of the mineralocorticoid receptor—beyond aldosterone

When I.S. Edelman characterized the mineralocorticoid receptor, he had difficulties to publish the finding because the receptor was orders of magnitudes more sensitive to cortisol than to aldosterone. This paradox has subsequently been clarified by the demonstration of pre-receptor metabolism, i.e. local conversion at the receptor site of cortisol to its metabolite cortisone. This conversion is catalyzed by 11-beta-hydroxysteroid dehydrogenase-2 (11-beta-HSD-2), malfunction of which is associated with several forms of hypertension, including hypertension of the elderly [10]. Recent studies concluded that an ancient steroid receptor had been ‘highjacked’ by aldosterone after transition of vertebrates from the sea to land life when more stringent conservation of sodium was required.

More relevant for the recent ‘epidemic’ of hypertension associated with high aldosterone concentrations is the observation that visceral obesity is associated with elevated aldosterone [11], mainly because human visceral adipocytes secrete potent mineralocorticoid-releasing factors [12] presumably EKODE [epoxy-9keto-10trans-octadecenoic acid] [13]. This may explain the observation in the Framingham study that plasma aldosterone concentration was...
significantly correlated with the risk of onset of the metabolic syndrome [14]. In an animal model of the metabolic syndrome, aldosterone caused podocyte injury [15] with proteinuria responsive to treatment with eplerenone [16] and tempol [17] pointing to a role of oxidative stress.

Aldosterone actions—beyond the classical mineralocorticoid receptor

The classical concept of aldosterone was that aldosterone synthesized in the adrenal cortex acted in an endocrine fashion on transport epithelial (distal nephron, colon, salivary glands, sweat gland), promoting vectoral transepithelial Na⁺ transport mediated by SGK-1 (serum and glucocorticoid-inducible kinase).

This concept has now been expanded in two ways. First, non-genomic effects have been identified mediated by the interaction of aldosterone with a hypothetical plasma membrane receptor, the time frame of such actions is seconds (and not hours as necessary for genomic effects), and these effects are not inhibited by the transcription inhibitor actinomycin D [18].

Second, apart from the classical effects of aldosterone on transport epithelia, non-classical effects on interstitial tissues, specifically endothelial cells, fibrocytes, have more recently been identified as well.

Aldosterone has thus become a hormone not only involved in blood pressure control but also involved in cardiovascular and renal target organ damage. These past and novel roles have recently been summarized as ‘the good, the bad and the ugly’ [19].

The good: aldosterone causes sodium retention and potassium homeostasis, thus avoiding hypotension in land-living species.

The bad: in the presence of high-salt intake, aldosterone causes persistent hypertension resulting in blood pressure-dependent target organ damage.

The ugly: in a permissive milieu, also tightly linked to high-sodium intake, even normal aldosterone concentrations promote blood pressure-independent target organ damage caused via inflammatory or pro-fibrotic pathways involving oxidative stress, activation of NF-kappa-B, AP-1, NADP-oxidase, ICAM, VCAM and others.

Aldosterone—blood pressure-independent target organ damage

A most elegant experiment in human endothelial cell monolayer cultures was reported by Oberleithner [20]: when the extracellular sodium concentration was increased above a threshold of 135 mmol/mM, endothelial cell stiffness increased in the presence of aldosterone but this could be prevented by adding the mineralocorticoid receptor antagonist eplerenone. Increased endothelial cell stiffness was mediated by interaction of aldosterone with a hypothetical plasma membrane receptor. In the presence of high-sodium concentration, its activation decreased nitric oxygen (NO) release, thus altering endothelial cells and the neighbouring vascular smooth muscle cells’ function causing increased vascular stiffness and resistance [21]. A correlation between indices of vascular stiffness and aldosterone-to-renin ratios was for instance found in the Framingham offspring study [22].

Observations in humans are in line with this pathomechanism. For instance, Mahmud [23] showed that in hypertensive patients, blood pressure was similarly lowered with either spironolactone or a thiazide. While both drugs reduced blood pressure, only spironolactone but not the thiazide reduced the pulse wave velocity; this effect was blood pressure independent, pointing to direct endothelial cell and vascular actions of aldosterone. Such direct effects have been documented in vessels, in heart tissue [24] and in kidneys [25]. It is somewhat controversial whether ectopic production of aldosterone outside of the adrenal gland occurs in healthy humans, but it was documented in the heart of patients with cardiac failure [26].

Such blood pressure-independent and natriuresis-independent effects explain the benefit observed with the effect of non-natriuretic doses of spironolactone or eplerenone in patients with severe heart failure, i.e. in the RALES [27] and EPHEBUS [28] studies.

Aldosterone and progression of renal disease

In malignant nephrosclerosis of the SHRsp on high salt [29] or in rats double transgenic for the human renin and angiotensinogen genes [30] as well as in a model of malignant nephrosclerosis [31], manoeuvres such as adrenalectomy or administration of eplerenone or spironolactone prevented renal and vascular tissue damage.

Studies in animals with renal failure showed hyperplasia of the zona glomerulosa [32] and a 10-fold increase in plasma aldosterone [33] of the adrenal gland, while conversely adrenalectomy reversed proteinuria and structural lesions in the subtotally nephrectomized rat [34]. The decisive experiment was performed by Greene and Hostetter [33]: after subtotal nephrectomy, RAS blockade (ACE inhibitors plus ARB) caused a striking decrease of proteinuria. Additional administration of aldosterone, however, increased proteinuria again by a factor of almost 10. Spironolactone does not only prevent glomerular lesions [33] but also causes even regression of established glomerulosclerosis [35].

In all these studies, animals were on a high-sodium diet and such adverse effects of aldosterone occur only under high salt conditions. The importance of salt intake is beautifully illustrated by an Indian tribe in the Amazonas, the Pima Indians, who live on minimal sodium intake (natriuresis 1 ± 1.5 mmol/day): they have low blood pressure values (102/62 mmHg) despite serum aldosterone concentrations above the usual concentration in Conn syndrome (85.6 ± 78 ng/dl [36]. In animal experiments, high-salt environment is found to be associated with an inflammatory response (NF-kappa-B), diminished nitric oxide release as well as inflammatory infiltrates and tissue remodelling [37].
Against this background, Bomback et al. [38] recently asked—somewhat tongue in cheek—‘Renal aspirin—will all patients with chronic kidney disease one day take spironolactone?’—suggesting that much of the extrarenal pathology in uremic patients is caused by the ‘ugly’ effects [19] of high aldosterone in a high-salt environment.

Aldosterone is not only of interest in end-stage kidney disease but also plays a role in the progression of chronic kidney disease. An adverse effect of aldosterone on the kidney is suggested by the observation that at comparable levels of blood pressures, patients with primary aldosteronism have more pronounced proteinuria than patients with essential hypertension [39]. In patients with primary kidney disease, Ruggenenti et al. as well as Walker found a correlation between aldosterone concentrations and deterioration of renal function. [40,41]. Plasma aldosterone concentrations are elevated early on when GFR is >70 ml/min [42]. These findings raised the obvious question whether spironolactone—independent of blockade of the renin–angiotensin system—would be another agent suitable to limit renal injury. In patients with proteinuria >1 g/24 h, despite ACE inhibitor treatment, Chrysostomou and Becker [43] added 25 mg spironolactone to the regimen and observed an average reduction of proteinuria by 54% without significant change in blood pressure or creatinine concentration. This observation has been confirmed by others, particularly in patients with type 2 diabetes [44].

**Therapy-resistant hypertension—the role of mineralocorticoid receptor blockade**

Many major hypertension intervention trials came to the conclusion that a large proportion of patients fail to achieve the goal blood pressure proposed by the Joint National Committee VII [45]. Progressively higher proteinuria is found in patients with resistant hypertension at progressively higher tertiles of salt intake and this is paralleled by progressively higher urinary aldosterone excretion [46]. In a cohort of patients with resistant hypertension, plasma aldosterone/renin ratios and urinary aldosterone excretion rates were higher than in controls and this was associated with biomarkers (ANP, BNP) pointing to hypervolaemia [47].

In ‘resistant hypertension’ defined by the Joint National Committee VII [48] as ‘failure to achieve goal BP when a patient adheres to maximum-tolerated doses of three anti-hypertensive drugs, including a diuretic’, the addition of spironolactone as the fourth line treatment is highly effective as recently again illustrated by the ASCOT trial [49].

**Proteinuria ‘escape’—the role of aldosterone and consequences for treatment of renal patients with proteinuria**

In proteinuric patients treated with ACE inhibitors or ARBs, protein excretion usually decreases, but after 1–3 years a secondary increase of proteinuria (‘escape’) is observed in a large proportion of patients. Such ‘escape’ is paralleled by an increase in the initially lowered plasma aldosterone concentration [50] and is associated with more rapid loss of GFR as documented in several studies on diabetic nephropathy [51]. The recently unpublished paediatric ESCAPE study showed that despite excellent blood pressure control, 50% of patients on intensified blood pressure control and RAS blockade were back again after approximately 3 years at baseline protein excretion.

Intervention studies indicate that prevention of aldosterone escape is possible to some extent by intensifying RAS blockade as also shown in patients with congestive heart failure [52]. In diabetic nephropathy, following the communication of Sato et al. [53], reversal of proteinuria escape by adding spironolactone has been confirmed by numerous investigators. Experimental studies showed that aldosterone and eplerenone restored reduced expression of podocin by podocytes [17]. In patients with nephrotic proteinuria on ACE inhibitors plus ARBs, addition of spironolactone (but not addition of thiazides) caused a further decrease of proteinuria unrelated to blood pressure [54]. Unfortunately, this strategy is associated with a substantial risk of hyperkalaemia, first described by Schepkens et al. [55], which necessitates careful instruction and supervision of such patients.

**Conflict of interest statement.** None declared.

**References**

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