Aldosterone in Uremia – Beyond Blood Pressure

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Abstract
Aldosterone was in the past considered only as a prohypertensinogenic agent. It has recently become clear that apart from the classical endocrine action, i.e. causing blood pressure elevation as a result of salt retention, aldosterone has numerous blood-pressure-independent actions on nonepithelial tissue. Under conditions of high salt concentration, aldosterone is injurious to the kidney, heart and vasculature. Of particular interest are recent observations that aldosterone is a permissive factor for the effect of minor increases in plasma sodium concentration on endothelial cell dysfunction. Despite surprising effects of aldosterone blockade on blood pressure of anuric dialysis patients, the potential role of mineralocorticoid receptor blockade in dialysis patients is currently unclear and requires controlled investigation to define the risk of potential hazards, specifically hyperkalemia.

Introduction
Since the classical paper of Conn \cite{1} in 1955, the relation of adrenal adenoma or bilateral hyperplasia to hypertension is well recognized. Recently there has been a controversy whether we are currently confronted with an unrecognized epidemic of primary aldosteronism because up to 20–30\% of hypertensive patients have values above the (arbitrary) plasma aldosterone/renin ratio. The data of the Framingham study suggest that progressively higher blood pressure values and prevalence rates of hypertension are found in progressively higher quartiles of serum aldosterone concentration \cite{2}, arguing for the following hypothesis: the higher the aldosterone concentration (at least under the present conditions of high salt consumption), the greater the risk of hypertension. Animal experiments provided convincing evidence for this assumption \cite{3}: genetic manipulation to increase the activity of aldosterone synthase was associated with normal blood pressure on a low-salt diet, but significantly increased blood pressure and target organ damage on a high-salt diet.

While sodium is a permissive factor, the blood pressure effect of aldosterone does not necessarily require changes in sodium balance. In anuric hemodialysis patients, Gross et al. \cite{4} showed that 50 mg of spironolactone decreased systolic blood pressure by 11 mm Hg, remarkably without any hyperkalemia; this observation indicates that under these conditions aldosterone had affected blood pressure by a direct effect on vascular resistance.

Activation of Mineralocorticoid Receptor – Signals Other than Aldosterone

Animals living in salt water have no aldosterone, but a precursor of the mineralocorticoid receptor which is stimulated by glucocorticoids. This receptor was later ap-
Apparently highjacked by aldosterone once animals conquered the continents with scant salt supply. The mineralocorticoid receptor can be strongly stimulated by cortisol, but this is normally prevented by prereceptor metabolism in the synaptic cleft, i.e. the conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase 2. Under certain conditions, cortisol is increased in the synaptic cleft, specifically during inflammation, metabolic syndrome or altered redox potential; cortisol then activates the mineralocorticoid receptor, and although the receptor is activated by the ‘wrong’ ligand, the downstream effects can still be successfully antagonized by mineralocorticoid receptor antagonists.

One observation is particularly relevant for the nephrologist. Visceral fat of obese individuals or animals releases a factor with the name EKODE (epoxy-keto-oc-tadecenoic acid) [5] which activates aldosterone synthase in the adrenal cortex and stimulates aldosterone secretion independent of angiotensin II, adrenocorticotropin in the adrenal cortex and stimulates aldosterone secretion independent of angiotensin II, adrenocorticotropin and K⁺. Albuminuria (and presumably further renal damage in the metabolic syndrome) is caused by EKODE-stimulated aldosterone and responds to mineralocorticoid receptor blockade [6].

The emerging clinical implications of the role of aldosterone in the metabolic syndrome, renal sequelae and resistant hypertension have recently been elegantly summarized by Sowers et al. [7].

**Aldosterone Action – Beyond the Classical Actions**

The classical concept proposed that the transcription of aldosterone requires endocrine actions on vectorial transepithelial transport of transport epithelia, e.g. the distal nephron, colon, salivary gland or sweat gland.

It has become clear that the endocrine genomic effects of aldosterone are not its only actions. Elegant experiments provide clear evidence for nongenomic effects, amongst others also in the pre- and postglomerular arterioles of the kidney [8].

Apart from the classical effects on epithelial cells as targets, aldosterone exerts also nonclassical effects on interstitial tissues, specifically endothelial cells and fibroblasts [9] which are involved in fibrosis of the heart, kidney and vessels.

The various aspects of interaction between aldosterone and the cardiovascular system have recently been characterized as ‘the good, the bad and the ugly’ [10]:

- the good: sodium retention, avoiding hypotension;
- the bad: under high-sodium conditions, persistent hypertension and blood-pressure-dependent organ damage;
- the ugly: in a permissive milieu (e.g. inflammation), even at normal aldosterone concentrations, blood-pressure-independent target organ damage through inflammation, profibrotic pathways, oxidative stress, neural factor kB, activator protein 1, nicotinamide adenine dinucleotide phosphate oxidase, intercellular adhesion molecule, vascular cell adhesion molecule …

The human relevance of this is impressively illustrated by a recent study (LURIC trial) on subjects with coronary heart disease where aldosterone concentrations within the normal range were related to increasing hazard ratios of cardiovascular mortality.

These considerations prompted a recent comment in 'Renal aspirin: will all patients with chronic kidney disease one day take spironolactone?' [11].

**Aldosterone – Blood-Pressure-Independent Target Organ Damage**

In the past, nephrologists were concerned only about sodium balance. Sodium concentration was thought to be nearly constant and minor changes irrelevant. That the sodium concentration is not irrelevant was shown in patients with essential hypertension in whom a minor but highly significant elevation of plasma Na⁺ concentration was found [12]. In animal experiments, such minor elevations have been shown to increase sodium concentration in the cerebrospinal fluid [13] promoting the synthesis of cardiotonic steroids (i.e. digitalis-analogous endogenous steroids), increased blood pressure [14] and caused blood-pressure-independent cardiomyopathy and accelerated progression of kidney disease [15].

Recent studies of Oberleithner et al. [16] have carried this one step further: raising the extracellular sodium concentration from 135 to 160 mmol/l caused a gradual increase in endothelial stiffness, reduced nitric oxide production and caused endothelial cell shape change. The presence of aldosterone was permissive for this effect. This effect is mediated via amiloride-sensitive sodium channels [17]. From the perspective of the dialysis patient, it may therefore be quite relevant to watch not only the sodium balance and its impact on ‘dry weight’, but also the sodium concentration, one determinant of which is the dialysate sodium concentration. Arterial stiffness is a known complication of uremia. Of interest are therefore observations in essential hypertension. Al-
Aldosterone is a permissive factor for the above effect of Na⁺ on the vasculature. In hypertensive patients, the pulse wave velocity (as a marker of arterial stiffness) responded on the vasculature. In hypertensive patients, the pulse wave velocity (as a marker of arterial stiffness) responded

Numerous animal experiments showed that in the absence of a change in blood pressure, aldosterone receptor blockade reduced target organ damage in hypertensive animals, e.g. spontaneously hypertensive stroke-prone rats [19].

In the past, administration of spironolactone or other mineralocorticoid receptor blockers was considered to be strictly contraindicated because of the risk of hyperkalemia which is undoubtedly a serious problem [20, 21]. In the light of the above data [4], this issue requires reassessment in carefully conducted studies in dialysis patients.

Aldosterone-induced target organ damage is sodium-dependent. It is remarkable that a low-sodium diet or renal sodium loss completely prevent aldosterone-induced target organ damage, e.g. cardiac hypertrophy or cardiac fibrosis [22]. These considerations illustrate the wisdom of the nestor of our specialty, Belding Scribner, who fought until the end of his life for ‘the drug-free, salt restriction, ultrafiltration method of blood pressure control’ in dialysis patients [23]. Based on the above new finding, it appears possible that beyond blood pressure sodium restriction may even have major blood-pressure-independent target organ benefits [11].

References