

Salt and Aldosterone – Reciprocal and Combined Effects in Preclinical Models and Humans



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ABSTRACT

Primary aldosteronism is an endocrine disorder caused by excessive production of aldosterone by the adrenal glands, and is recognized as the most important cause of endocrine hypertension. With specific therapy, this type of hypertension is potentially curable. In the general population, high salt intake increases the risk for cardiovascular diseases like stroke. In populations with aldosterone excess, observational and experimental data suggest that aldosterone-induced organ damage requires a combination of high dietary salt intake and high plasma aldosterone, i.e., plasma aldosterone levels inappropriately high for salt status. Therefore, understanding the relationship between plasma aldosterone levels and dietary salt intake and the nature of their combined effects is crucial for developing effective prevention and treatment strategies. In this review, we present an update on findings about primary aldosteronism and salt intake and the underlying mechanisms governing their interaction.

Introduction

From an evolutionary perspective the renin angiotensin aldosterone system (RAAS) is designed to preserve sodium in a low-salt (sodium chloride) environment in order to maintain serum osmolality, plasma volume, and blood pressure (reviewed in [1]). In brief, stimuli such as a drop in renal perfusion pressure or reduced delivery of sodium at the macula densa trigger the secretion of renin from juxtaglomerular cells [2]. Of note, evidence also suggests an independent role for chloride in the regulation of renin release [3]. Renin as a protease then converts circulating angiotensinogen to angiotensin I. Angiotensin-I-converting enzyme on the surface of endothelial cells converts angiotensin I to angiotensin II. This peptide triggers the secretion of aldosterone by zona glomerulosa cells

of the adrenal cortex (reviewed in [4]). The secretion of aldosterone is also regulated through additional pathways: A low salt diet was demonstrated to increase aldosterone synthesis following hypomethylation of the *Cyp11b2* promoter in rats, suggesting that also epigenetic factors seem to be at play [5]. In pigs, a low salt diet increased the expression of VSNL1 in the zona glomerulosa as compared to a high salt diet [6]. VSNL1 is a calcium-sensing protein known to enhance baseline as well as angiotensin II-mediated aldosterone secretion [7].

Conversely, a challenge with a bolus of intravenous saline will suppress aldosterone secretion through inhibition of renin. This forms the basis of the saline suppression test used as confirmatory testing in the diagnosis of primary aldosteronism (PA) [4].

Further complexity is added by the observation of local, that is, tissue-resident RAA systems and alternative angiotensinogen derivatives, which stimulate their own receptors and exert partly opposite effects to the classical cascade [8].

Next to direct effects of angiotensin-II, the RAAS exerts its potency mainly via aldosterone-induced (re)absorption of sodium across epithelia like kidney tubular cells and colonic epithelial cells in addition to sweat glands [1]. Direct actions in non-epithelial cells like smooth muscle cells are increasingly recognized [9].

Renal target genes that are positively regulated by the mineralocorticoid receptor encompass subunits of amiloride-sensitive sodium channels (ENaC) and subunits of the Na^+/K^+ -ATPase, that is, structures designed to promote luminal sodium reabsorption and basolateral secretion [1]. Aldosterone-induced sodium absorption in the context of low environmental salt is also promoted in intestinal epithelial cells of the distal colon in a mineralocorticoid receptor-dependent manner involving the β - and γ -subunit of ENaC channels [10].

Traditional views hold that aldosterone-induced sodium (re)absorption results in expansion of plasma volume and increase of cardiac output and consecutive elevation of blood pressure. This was recently challenged by a study which reported that subsequent to sodium loading of aldosterone-infused rats an increase in systemic resistance was noted with a parallel decrease in cardiac output [11].

It has been convincingly demonstrated that sodium intake is associated with an increase in blood pressure [12] and an increased risk of stroke and cardiovascular disease [13]. To combat arterial hypertension current guidelines, therefore, recommend salt restriction approaches as lifestyle measures in all patients with arterial hypertension [14, 15]. The World Health Organization recommends 5 g of salt as maximum daily intake [16].

Primary aldosteronism (PA) compared to essential hypertension also is associated with a greater risk of stroke, coronary artery disease, atrial fibrillation and proteinuria, even after matching for age, sex and blood pressure grade [17]. It becomes evident that the combination of two factors (salt and aldosterone excess) constituting a cardiovascular risk of their own is likely to enhance cardiovascular morbidity and mortality.

Primary aldosteronism promotes salt intake by increasing the recognition threshold for salty taste. Following specific therapy [either mineralocorticoid receptor antagonist (MRA) therapy or adrenalectomy], a normalization of salt taste threshold was observed [18, 19]. At least part of this right shift in recognition threshold may be mediated through central effects of aldosterone on neurons of the nucleus of the solitary tract (NTS) which is a main central regulator of salt intake [20].

It has been known since the 1990s that it requires a high salt diet for aldosterone excess to cause hypertension and organ damage [21]. In contrast, indigenous cultures with very high aldosterone concentrations secondary to low dietary sodium intake (secondary hyperaldosteronism) are characterized by low blood pressure values and do not feature the traditional progressive increase in blood pressure with age [22].

Understanding the interaction between aldosterone and salt is crucial for developing effective prevention and treatment strategies. Therefore, this review aims to present the current knowledge

on primary aldosteronism and salt intake and their underlying mechanisms. Wherever possible we will try to focus on evidence from systems challenged with aldosterone excess and try to avoid discussing findings in normotensive or essentially hypertensive cohorts.

Setups to study the effects of mineralocorticoid excess (+/- salt)

One of the most studied rodent models for hypertension involves implantation of a DOCA pellet (deoxycorticosterone acetate, a mineralocorticoid precursor) in rats together with oral administration of salt (usually in the range of 1% NaCl) (reviewed in [23]). This system is sometimes augmented by uninephrectomy to impair renal sodium handling and induce profound hypertension. DOCA may be exchanged with aldosterone, which is then given continuously via a minipump through a subcutaneous route [24, 25]. Varying NaCl concentrations allow the researcher to study the downstream effect of mineralocorticoid excess (blood pressure, cardiac fibrosis, etc.) as a function of dietary sodium content.

In recent years, mouse models for endogenous aldosterone excess were developed and involve, amongst others, a gain of function mutation (R180Q) of the chloride channel gene *Clcn2* analogous to human familial hyperaldosteronism type II [26]; a *Clcn2* mutation yielding a higher open state probability (op/op) [27]; a mouse line with 50% increase of aldosterone synthase expression [28]; and a mouse model with a designer receptor exclusively activated by a designer drug (DREADD) expressed under control of the aldosterone synthase promoter [29], allowing to control the onset and duration of hyperaldosteronism.

Finally, patient cohorts with primary aldosteronism on diets with varying salt content are of high value to corroborate the findings from preclinical studies [30–32].

Evidence for salt-dependence of aldosterone-induced hypertension and organ damage

Not all aldosterone-mediated changes were investigated for dependence on sodium (inflammation, aortic stiffness, etc). However, most of the pathological effects seen in humans do happen on the background of a diet rich in salt, so a sodium-replete state can be safely assumed.

Arterial hypertension and cardiac damage

When rats on a low salt diet were administered aldosterone through minipumps, no significant elevations in blood pressure were noticed. In contrast, animals on a high sodium diet were rendered severely hypertensive through the same aldosterone infusion. These animals also developed left ventricular hypertrophy and perivascular fibrosis [21, 24]. Similar results were obtained through deoxycorticosterone in combination with a high salt diet [21]. Hypertension and myocardial fibrosis responded well to MRA therapy [24]. Myocardial fibrosis was shown to be independent of arterial hypertension, administration of potassium and left ventricular hypertrophy. Moreover, the blood pressure increase to aldosterone and salt was blunted after intracerebroventricular MRA administration [33].

A recent study demonstrated that rats remained normotensive on a low salt diet despite aldosterone infusion. After switching the

same animals to a high salt diet, blood pressure rose and stayed elevated [11].

Comparable results were reported in a rat model rendered hypertensive by administration of the NO synthase inhibitor L-NAME together with angiotensin II. Myocardial damage developed only in animals receiving a high salt diet and was blunted by MRA therapy. Again, potassium supplementation did not show an effect, allowing the conclusion that the cardioprotective effects of MRA were not mediated by potassium elevation but rather through antagonizing other effects downstream of MR activation. Of note, this rat model did develop arterial hypertension despite a low salt diet, underlining that L-NAME and angiotensin-II work through distinct pathways than aldosterone [34].

With respect to a putative mode of action for sodium, myocardial fibrosis in response to salt and mineralocorticoids seems to involve the NHE-1 (Na⁺/H⁺ exchanger isoform 1) [35, 36]. While one study reported additional antihypertensive effects of NHE inhibition [35], the other could not replicate this finding [36]. It is not clear whether sodium enters cells through the transporter or whether it is involved in downstream signaling of salt and mineralocorticoids.

Mice with mild *Cyp11b2* overexpression show an increase of blood pressure in response to increases in dietary salt content. Although aldosterone was suppressed by salt intake, the absolute levels were still greater than in wild type mice, confirming the interaction between salt intake and aldosterone to promote blood pressure increases [28].

A model of human familial hyperaldosteronism type II (FH-II), that is, a germline mutation in the chloride channel gene *Clcn2*, however, could not demonstrate further increase in arterial blood pressure in response to elevation of dietary salt (3.23% sodium): The group around Thomas Jentsch observed an additional increase in blood pressure exclusively in female mice when animals (both sexes) constitutively expressing the *Clcn2* op/op variant (higher open probability) received a high salt diet [27].

Using their innovative model of a Designer Receptors Exclusively Activated by Designer Drugs (DREADD) system expressing a human Gq protein-coupled receptor [activated only by the exogenous substance clozapine *N*-oxide (CNO)] under the control of aldosterone synthase, the Rainey group demonstrated that blood pressure increased only in animals with combined challenge of high salt diet and endogenous hyperaldosteronism. When hyperaldosteronism was turned off (i. e., withdrawal of the ligand CNO), blood pressure gradually normalized after 10 days despite persisting high salt diet, along with adequate restoration of circadian dipping. Aldosterone was elevated in a manner related to duration of CNO exposure [29]. These data are as close as possible to patients with primary aldosteronism who underwent adrenalectomy but continue their typical sodium-rich diet and provide reassurance with respect to the potential for postoperative normalization of blood pressure. Further studies might determine the critical time of exposure to endogenous hyperaldosteronism after which blood pressure cannot return to normal again. Likewise, the impact of salt restriction in mice exposed to CNO and in mice after CNO withdrawal should be examined. Also, the dependence of organ damage measures on dietary salt content in CNO-treated transgenic animals remains to be determined.

The group around Michael Stowasser described cardiovascular changes in a cohort of patients with familial hyperaldosteronism type I (FH-I): Despite not (yet) hypertensive, signs of left ventricular hypertrophy were apparent due to high aldosterone levels. These patients in addition to increased aldosterone and suppressed renin levels showed 24-hour urinary sodium excretion compatible with high salt intake (corresponding to an estimated salt intake of 7.6 g/d) [32]. The results underline that in contrast to the above-mentioned indigenous tribes with low salt intake, aldosterone levels inappropriate for salt status do cause cardiovascular damage even in the absence of arterial hypertension.

Taken together, these preclinical and clinical findings convincingly suggest that MR-mediated myocardial hypertrophy and fibrosis in PA strongly depend on dietary salt intake.

Vascular damage

In a similar manner to the changes reported in heart and kidneys, aldosterone and salt given to rats resulted in MR-dependent accumulation of fibronectin in the aorta with a parallel increase in carotid artery stiffness [37]. Arterial stiffness is accepted as a clinical hallmark in patients with PA [38, 39].

Angiotensin II and salt induced coronary artery fibrinoid necrosis and perivascular inflammation as well as expression of the inflammatory markers COX2 and osteopontin in a manner dependent on stimulation of MR by systemic aldosterone [40].

As an exception, one study found that aldosterone may induce vascular remodeling via endothelin A (ETA) receptors and reactive oxygen species even in the absence of salt loading [41]. Why aldosterone in this context did not require elevated salt concentrations remained unresolved.

Rocha and colleagues reported that in contrast to salt loading alone, aldosterone plus 1% NaCl resulted in remodeling (medial thickening) of coronary arteries with perivascular leukocyte infiltrations which they termed “vascular inflammatory phenotype” [25]. Functionally, aldosterone and salt mainly impair endothelial capacity to generate nitric oxide in a manner involving decreased glucose-6-phosphate dehydrogenase activity, resulting in increased vascular levels of reactive oxygen species [42]. Decreased release of NO by endothelial cells exposed to aldosterone was also triggered by increased concentrations of sodium in the culture medium. These led to progressive stiffening of the endothelial cell cortex in an ENaC-dependent manner and reduced NO production [43]. These changes may well explain endothelial dysfunction which has been described in many cohorts of patients with PA [44–48].

Of interest, when atheroprone ApoE^{-/-} mice were fed an atherogenic diet together with administration of aldosterone they developed increased plaque size and plaque inflammation probably via endothelial ICAM-1 induction. In this context, the hypercholesterolemia of ApoE^{-/-} mice may have been sufficient to inflict endothelial damage and, thus, did not require additional salt loading for aldosterone to enhance plaque formation [49].

In summary, for vascular damage, although some data exist that sodium may be dispensable, most data support that also for this end organ damage a double hit by salt and aldosterone is required.

Renal damage

In rats, continuous infusion of aldosterone together with 1 % NaCl via drinking water resulted in arterial hypertension, proteinuria, glomerular damage as evidenced by an increased mesangial matrix and glomerular hypercellularity. These effects could be blunted using MRA or antioxidant substances [50]. Other effects on the kidneys included tissue fibrosis and accumulation of macrophages. The pathological changes responded to MRA therapy [51].

Another study in rats demonstrated that aldosterone plus 1 % NaCl resulted in severe arterial hypertension which partly responded to MRA therapy. A dietary content of 1 % NaCl alone did not cause hypertension. Likewise, renal pathological changes by aldosterone/salt treatment such as glomerulosclerosis, vascular sclerosis and tubular dilation as well as mRNA levels of proinflammatory genes were attenuated by MRA but did not revert to normal. Unfortunately, monotherapy with aldosterone was not studied so one can only speculate about the putative effect of salt restriction in combination with MRA [52].

Our group could show that salt restriction in patients with medically treated primary aldosteronism resulted in a reduction of urinary albumin excretion which just missed the significance threshold ($p = 0.057$) and, thus, may suggest that also for glomerular injury the combination of salt and aldosterone is necessary [31].

Interactions between salt and aldosterone to promote mineralocorticoid-induced organ damage

Several mechanisms could potentially explain why salt loading is required for mineralocorticoid pathology.

Local RAAS activities

Evidence from rats suggests that high salt may promote local cardiac aldosterone synthesis. This occurred despite physiological suppression of renin and aldosterone in response to dietary salt loading. Sodium-loaded rats experienced cardiac hypertrophy despite normotensive blood pressures [53].

While salt-loaded rats exhibited the expected reduction in circulating angiotensin-II and aldosterone, tissue levels of these hormones increased with concomitant evidence of increased intracellular oxidative stress [54]. Extra-adrenal production of aldosterone was suggested to occur in cardiovascular tissues such as endothelial [55, 56] and smooth muscle cells [56, 57].

These findings highlight how local RAAS activities may link salt excess to the opposite effects of what one would expect from physiology and promote localized/compartimentalized aldosterone excess in the context of salt excess.

Endogenous ouabain-like compounds

Circulating inhibitors of Na^+/K^+ -ATPase, termed cardiotonic steroids (CS), have been found to respond to changes in dietary sodium, with a small increase in diuretic-induced salt depletion and a strong increase following salt loading [58]. In hypertensive rat strains and humans with arterial hypertension these inhibitors were detected at increased concentrations [59]. The substance marinobufagenin, one of these steroids, has been described to be secreted from adrenocortical cells [60]. Salt-dependent adrenocortical secretion of CS was promoted as a potential explanation for salt dependence of mineralocorticoid damage [61] given the observation

that high plasma aldosterone levels are paralleled by high plasma CS in patients with essential hypertension [62]. So far, a small study on 20 patients with PA reported that indeed plasma marinobufagenin was increased in aldosterone excess [63]. The observation that a combined challenge with salt and aldosterone led to an increase in systemic vascular resistance [11] would be compatible with being mediated by a vasoconstrictor substance such as marinobufagenin [64]. Also, endogenous ouabain-like substances have been described to generate reactive oxygen species and activate pro-inflammatory NF- κ B signaling [65].

Reactive oxygen species

A rat model revealed a role for reactive oxygen species (ROS)-induced renal MR activation and nuclear translocation which bypassed aldosterone suppression in the context of a high salt diet to mediate proteinuria and glomerular/podocyte injury [66]. The concept of ROS-induced MR activation was further validated in cardiomyocytes by the same group [67].

Salt increased infarct size and apoptosis in experimental myocardial infarction compared to water, even with adrenalectomy. MR antagonism attenuated infarct size and apoptosis.

In the same study, a protective effect of antioxidant treatment in preventing mineralocorticoid- or glucocorticoid-induced excessive ischemia/reperfusion injury was demonstrated. The results suggested that reactive oxygen species may alter cellular redox potential and allow for activation of MR by cortisol (or corticosterone in rodents) [68].

In vascular smooth muscle, increasing culture medium concentrations of sodium led to an augmentation of aldosterone-induced expression of NADPH oxidase and consequent superoxide production. Eplerenone was able to attenuate the sodium-induced enhancement of NADPH oxidase expression, while high sodium alone was insufficient to cause increased NADPH oxidase expression [69].

Gut microbiome and inflammation

The contribution of salt to a change in gut microbiota has been demonstrated using salt sensitive rat strains [70]. The same rat model revealed that high salt alters the gut microbiome and changes the production of short chain fatty acids [71]. Supporting evidence also exists from human hypertensive patients [72]. Consequently, the contribution of gut microbiota to arterial hypertension has also been recognized in the recent version of the ESH guidelines [14]. It is noteworthy that a small study on patients with PA showed the gut microbiota to be altered in PA, with a shift towards species producing less short chain fatty acids and towards species associated with more inflammation [73].

Mineralocorticoid-induced inflammation in contrast has been observed for many decades in preclinical models [25, 40, 51] as well as recently in humans with PA [74]. Preclinical models provide evidence for the requirement of salt loading in order to induce perivascular inflammation [34].

Evidence is accumulating that increased dietary salt intake by itself can also promote inflammation and arterial hypertension in a manner involving TH_{17} cells (reviewed in [75]). One could hypothesize that, possibly again through inflammation-associated reactive oxygen species and MR oxidation, dual triggering of inflammation is necessary to cross a threshold for mineralocorticoid-mediated

end organ damage. Inflammation may also be seen as the link between changes in gut microbiota and aldosterone/salt-induced organ damage. Indeed, a mouse model yielded links between salt sensitive hypertension, gut dysbiosis and an aberrant response of TH₁₇ cells [76].

It seems as if reactive oxygen species with subsequent redox imbalance constitute the final pathomechanistic steps in the dual hit by salt and aldosterone (► Fig. 1). Of note, ROS are a common denominator of endogenous ouabain-like compounds, activation of local RAAS, and inflammation, whether mediated through alterations in gut microbiota or not. If indeed ROS turn out to be the final pathway to hypertension and organ damage by salt and aldosterone, all efforts should be made to combat them, for example, by developing conjugates of MRA and antioxidant substances. These conjugates might provide localized protection of the MR from oxidation and thereby exert the dual effect necessary to combat the pathological sequelae of a dual hit by aldosterone and salt.

Salt restriction as a therapeutic approach to primary aldosteronism

Systematic reviews demonstrated the power of salt restriction to even reduce blood pressure in normotensive probands. The anti-hypertensive effects extended across a range of subgroups defined by age, sex, baseline blood pressure and ethnicity [77]. In recent data, a linear correlation between the salt intake and blood pressure reduction was noted [12]. Likewise, a linear relationship between overall adjusted mortality risk and sodium intake was demonstrated in the TOHP I and TOHP II collectives [78]. An upper limit of 5 g salt intake/day is recommended by the World Health Organization [16]. The UK-based NICE guidelines issued a goal of 3 g/day for adults to be achieved by 2025 [79].

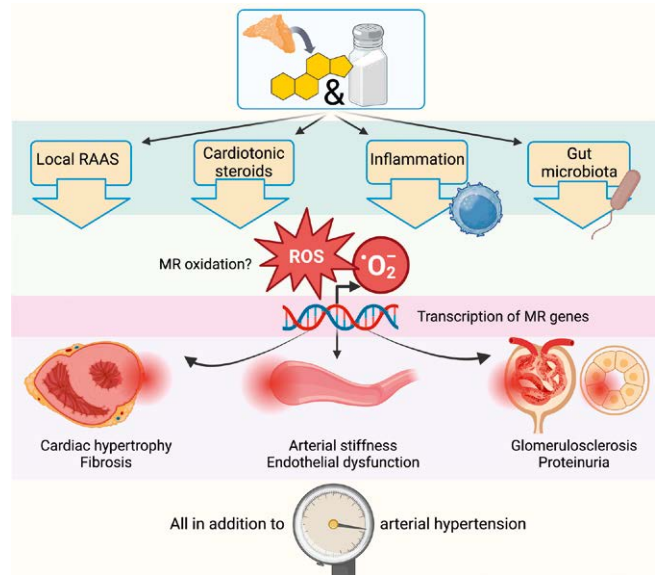
Despite the wealth of data in populations with essential hypertension, only a handful of studies exist which support the implementation of salt restriction efforts into the therapeutic approach to patients with PA.

A small study described normalization of the circadian blood pressure profile in patients with PA after short term salt restriction (1–3 g/d) [30].

Another study examined the relationship between MR activity and the response of circulating renin to dietary salt. Following 6 months of MRA therapy for PA, an inverse relationship between changes in dietary salt intake and changes in renin concentration was observed. The authors proposed that inadequate MR blockade permits renin levels to be suppressed by high dietary salt intake. They suggest salt restriction as add-on therapeutic approach in patients with PA whose renin is not stimulated on MRA [80].

An observational study reported greater reduction in left ventricular mass index in patients with PA who were able to reduce their sodium intake by more than 10% following specific therapy for PA (either surgery or initiation of MRA). These findings indicate that salt restriction may speed up recovery from end-organ damage [81].

Our group noted further improvement of already well-controlled systolic blood pressure values in medically treated patients with PA after 12 weeks of moderate salt restriction alongside other favorable changes (loss of body weight, antidepressant effect). The antihypertensive effect equated to a full dose of an additional an-



► Fig. 1 Summary of the putative mechanisms for the combined effects of aldosterone and salt. Local RAAS, cardiotonic steroids, inflammation and changes in gut microbiota are caused by either aldosterone or salt or both in combination. The aforementioned events all culminate on the generation of reactive oxygen species. These, in turn purportedly oxidate and activate the mineralocorticoid receptor, leading to a transcription of MR-dependent genes and downstream cardiac, vascular, and renal damage as outlined in the manuscript. (Created with BioRender.com) [rerif].

tihypertensive drug. One key aspect of the study was to maximize adherence by a convenient setting, which is why sodium restriction was kept moderate and self-paced via the help of a dedicated smartphone app. No apparent side effects such as increase in catecholamines, occurrences of hyponatremia or hypotension or even syncope were noted [31].

The most recent ESH guidelines for the treatment of arterial hypertension support the use of potassium supplementation [14]. Salt substitution to replace sodium with potassium as done in the SSaSS study [82] might be an amenable new therapeutic strategy to facilitate the adoption of a diet lower in sodium.

Conclusion

Preclinical and clinical data suggest that patients with PA are exquisitely salt sensitive. All the current data do not suggest that salt restriction in PA might impose harm. Rather, they call for a routine implementation of dietary counselling with regular reinforcement to restrict salt intake in patients with PA, particularly in those who are medically treated. Also, it would certainly help to promote adherence to dietary salt restriction in aldosterone excess if the precise neural mechanisms and brain centers on which aldosterone exerts its enhancement of salt appetite were known.

Moreover, future trials should address whether targeting inflammation and ROS, ideally guided by a certain cytokine or immune cell profile, or the gut microbiome (or just substituting microbiota-derived fatty acids) might be a clinically worthwhile study aim.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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