

Salt Appetite and its Effects on Cardiovascular Risk in Primary Aldosteronism



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ABSTRACT

First described in 1955 by Jerome W. Conn, primary aldosteronism (PA) today is well established as a relevant cause of secondary hypertension and accounts for about 5–10 % of hypertensives. The importance of considering PA is based on its deleterious target organ damage far beyond the effect of elevated blood pressure and on PA being a potentially curable form of hypertension. Aside the established contributory role of high dietary salt intake to arterial hypertension and cardiovascular disease, high salt intake is mandatory for aldosterone-mediated deleterious effects on target-organ damage in patients with primary aldosteronism. Consequently, counselling patients on the need to reduce salt intake represents a major component in the treatment of PA to minimize cardiovascular damage. Unfortunately, in PA patients salt intake is high and far beyond the target values of 5 g per day, recommended by the World Health Organization. Insufficient patient motivation for lifestyle interventions can be further complicated by enhancing effects of aldosterone on salt appetite, via central and gustatory pathways. In this context, treatment for PA by adrenalectomy results in a spontaneous decrease in dietary salt intake and might therefore provide further reduction of cardiovascular risk in PA than specific medical treatment alone. Furthermore, there is evidence from clinical studies that even after sufficient treatment of PA dietary salt intake remains a relevant prognostic factor for cardiovascular risk. This review will focus on the synergistic benefits derived from both blockade of aldosterone-mediated effects and reduction in dietary salt intake on cardiovascular risk.

Introduction

Large observational studies and clinical trials have shown that excessive dietary sodium intake, mainly consumed as sodium chloride (salt), is an important trigger for hypertension and cardiovascular disease (CVD) [1–4]. Therefore, a low sodium diet is an important component of the preventative strategy for reducing the risk of CVD, especially in patients suffering from hypertension [5]. When it comes to ambition and reality there is a huge gap, which is not only ascribable to the well-known lack of self-motivation for lifestyle changes in those patients but can be attributed to the extrinsic fact that salt is still used in great quantities as an important preserving agent and

taste enhancer in Western food industry. As people especially in Western societies consume more and more processed foods it is not surprising that the latter account for about 80% of daily salt intake and leaving only the remaining 20% to the direct control of patients, which illustrates the limited nature of dietary approaches. This could be why daily salt consumption in Western societies remains with about 10 g per day much higher than recommended by the World Health Organization (WHO) [6–10].

As aberrance from physiological ranges of plasma sodium concentration causes relevant health problems like cerebral edema, plasma sodium concentration is strictly regulated. One of the main

regulators is the steroid hormone aldosterone, which is synthesized in the zona glomerulosa of the adrenal cortex and acts predominantly via the epithelial sodium channel (ENaC) in the distal nephron, as a physiologic regulator of water and salt homeostasis to maintain stable blood pressure. In case of primary aldosteronism (PA), the most frequent cause of endocrine hypertension, excess of aldosterone inappropriately high for salt status, results in target organ damage far beyond the effect of blood pressure changes [11–18]. Hence this review focuses on the current knowledge of the interaction of aldosterone and dietary salt intake as well as their impact on cardiovascular risk.

Dietary salt intake in PA: where are we now?

The negative effects of a high salt diet on hypertension and cardiovascular risk in general are common consent [1–4]. Nevertheless, from time to time counterintuitive findings are published, these possibly influenced by methodological flaws especially in the way how dietary salt intake was estimated [19–21]. Based on the well-known negative effects of high salt diet and a general awareness that Western style diets are unhealthy one should assume that PA patients, from a psychological point of view, consume salt in a (very) moderate manner. But what is moderate? In general conditions ~1 g per day of dietary salt is supposed to be sufficient and 5 g per day are recommended as upper limit by the WHO especially in patients with hypertension [6, 10, 22]. This is also based on data about our ancestors who consumed diets with an estimated salt content of ~1 g per day for hundreds of thousands of years. Interestingly it was no longer than about 5000–10 000 years ago, with the advent of farming that the addition of salt to food began [23, 24]. Unfortunately in this case, the low spontaneous mutation rate of DNA leaves us with the mismatch of a genetic background selected for survival under conditions of low salt intake and the very recent appearance of dietary salt abundance [24].

Consequently, patients with PA might be particularly vulnerable in a high salt environment, given that aldosterone excess further stimulates salt reabsorption and is also suspected to increase dietary salt intake. The latter finding could explain why several studies have shown that estimated dietary salt intake in PA patients is much higher than recommended [25–28]. For instance in a recent post-hoc analysis from the German Conn's Registry we could show that PA patients have daily salt intake, estimated by 24-hour urinary sodium excretion, amounting to 11.9 g in men and 9.4 g in women a consumption of salt which is at least as high as the German median of 10.0 g in men and 8.4 g in women and doubles the target values initiated by the WHO [6, 29, 30].

Does aldosterone impact dietary salt intake?

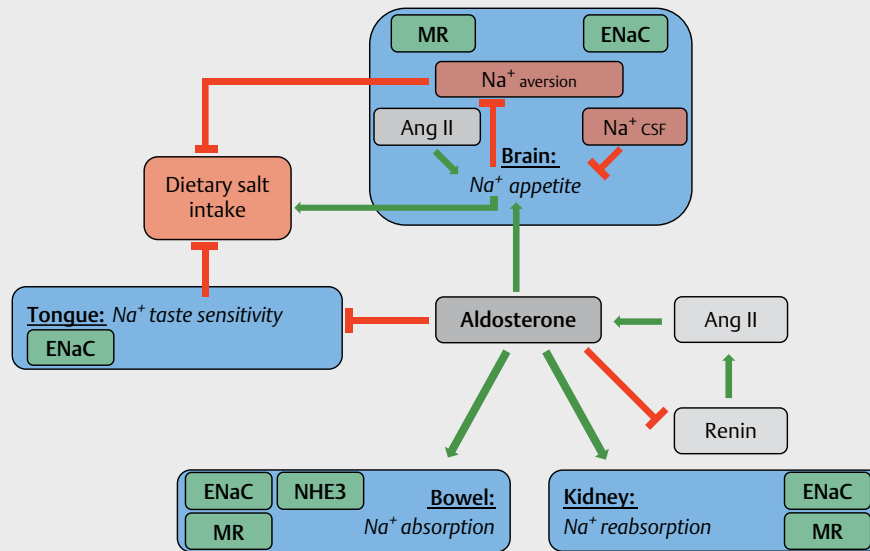
It is well known that aldosterone is one of the key regulators of salt and water homeostasis. Hereby salt loss is a strong stimulus for the release of aldosterone from the adrenal glands, although plasma sodium levels are usually within the physiological ranges [31]. Beside its salt retaining effect in the distal nephron of the kidney, where it leads to sodium reabsorption, aldosterone has also been shown to modulate salt appetite. Two major mechanisms are discussed: the impact of aldosterone on sodium sensing via ENaC in the tongue and direct aldosterone action on the brain as there the mineralocorticoid receptor (MR) is widely expressed.

We know from rodent studies that adrenalectomy causes renal salt loss and that administration of mineralocorticoids such as deoxycorticosterone (DOC), a precursor of aldosterone, or aldosterone at high doses increases salt intake in adrenalectomized as well as adrenal-intact rats, with the latter showing higher salt intake at comparable doses of DOC [32–36]. Furthermore, it could be shown that administration of aldosterone either to the forebrain or to the hindbrain increased sodium intake in rodents. This effect could be blocked by pretreatment with intracerebroventricular administration of MRA or antisense oligodeoxynucleotides against the MR but not against the glucocorticoid receptor (GR) [32, 37–39]. Francis et al. showed a faster reduction of salt intake following cerebroventricular versus intraperitoneal administration of spironolactone [40]. Changes in sodium intake were reported to occur rapidly (after 15 min) following DOCA administration into the amygdala which is in accordance with data from humans [38, 41]. This strongly argues for central aldosterone effects presumably via the MR in the regulation of salt appetite [42].

One of the most intensively studied areas in the brain is the hippocampus. Here the MR and the GR are widely expressed [43]. However due to the lack of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which inactivates cortisol to cortisone, the selectivity of the MR is quite low for aldosterone regarding the 100-fold higher concentration of cortisol [44]. Both steroids, however, show equivalent affinity to the MR, indicating that in tissues like the hippocampus the overwhelming majority of MR is occupied by glucocorticoids. Therefore, under physiological conditions the hippocampus seems to have only little effect on the aldosterone-mediated modulation of salt appetite, and this may be dose dependent. To our knowledge, there are only a couple of areas in the brain in which the MR and 11 β -HSD2 are co-expressed resulting in a high selectivity for aldosterone action on the MR. These are mainly the nucleus of the solitary tract (NTS), which could be shown to play an important role for salt intake under aldosterone stimulation [37, 43, 45–47]. In this context brain-specific knockout of 11 β -HSD2 was shown to increase sodium intake in mice, which suggests that under these conditions salt appetite may also be regulated by glucocorticoids [48]. Apart of that baroreceptors and other neural and endocrine signals are considered to modulate aldosterone-induced salt appetite but in total the exact mechanisms are still not fully understood and there is a lively debate on the role of aldosterone and the MR in the brain with also controversial findings [45, 49–52].

Besides the kidney, ENaC is also expressed in the gustatory system, namely in the taste buds of the tongue. Knockout of ENaC- α in taste-receptor cells resulted in almost complete loss of salt attraction in contrast to water in mice [53]. On the other hand, DOC-treated rats showed an increase in saline preference and even a loss of aversion against hypertonic sodium concentrations [32]. In line with these findings Sakamoto et al. reported a decrease in amiloride-sensitive salt taste nerve responses in aldosterone/sodium chloride treated rats, which could be a mediator for the better palatability for hypertonic sodium chloride solutions in rodents favoring higher salt intake under these circumstances (► Fig. 1) [54].

We have studied the effects of aldosterone on gustatory sodium detection in humans using sodium chloride serial dilution in patients with PA and essential hypertension. For this purpose, 10 different solutions of sodium chloride diluted in distilled water from



► **Fig. 1** Simplified model for the supposed effects of aldosterone on the regulation of salt intake: Aldosterone has several effector organs to regulate sodium homeostasis. In the brain it is supposed to operate via similar molecular mechanisms as established for the periphery, including activation of MR, to ultimately impact on sodium appetite. Aldosterone presumably also affects sodium sensing in the tongue, most likely via ENaC. In conjunction with the inhibition of sodium aversion in the brain and additive effects of angiotensin II these mechanisms allow for an increase in salt intake. Apart from that, higher plasma sodium concentration and respectively sodium concentration in the cerebral spinal fluid inhibits sodium appetite. To minimize salt loss aldosterone increases renal and intestinal salt (re)absorption. Ang II: Angiotensin II; Na^+_{CSF} : sodium sensor for the cerebral spinal fluid; ENaC: Epithelial sodium channel; Na^+ : Sodium; MR: Mineralocorticoid receptor; NHE3: Sodium-proton exchanger 3. Adapted from reference [42].

0.5 mmol/l to 256 mmol/l were used. Patients received a cup with either sample solution or distilled water. They were asked to keep the solution in their mouth for a few seconds and then to report on taste sensation. Preliminary results show that the recognition threshold, the concentration which was identified twice as salty tasting by the patients, is significantly higher in patients suffering from PA [55]. This is in accordance with the aforementioned animal studies and indicates the impact of aldosterone on salt tasting in patients with PA.

Synergistic effects of aldosterone excess and high salt diet

In the last decades, evidence has been gathered that deleterious cardiovascular and cerebrovascular effects in PA are (only) caused by aldosterone levels inappropriate for salt status [18, 56, 57]. Already in the 1990s, Brilla and colleagues showed that aldosterone administration causes myocardial fibrosis on a high sodium diet [16]. Similar results were reported by Young et al. who extended these analyses, whereas Rocha et al. could show that these effects could be blocked by administration of mineralocorticoid receptor antagonists (MRA) or adrenalectomy (ADX) [15, 17, 18]. Interestingly neither blood pressure increases, nor cardiovascular changes were caused by sodium deprivation even in the state of high aldosterone levels [16]. In accordance with these findings Funder reported New Guinea hill tribes with extraordinary low sodium intake of 2–3 mEq/day (~46–69 mg/day) who, despite very high aldosterone levels, showed normal blood pressure and no cardiovascular or renal damage [58].

The effect of high salt diet and inappropriate aldosterone levels on cardiovascular risk in PA was initially thought only to be related to blood pressure increase through fluid retention. However, animal studies have shown that blood pressure increases through administration of aldosterone are not necessarily caused by an increase in circulating volume [58, 59]. In another model for PA administration of eplerenone reduced cerebral and renal vascular damage without relevant effects on blood pressure levels [18]. In addition, Stowasser et al. have shown a significantly greater extent of cardiovascular damage in normotensive patients suffering from familial hyperaldosteronism type 1 compared with matched controls [60]. In this context there is substantial evidence for blood pressure-independent aldosterone-mediated tissue damage as also reported by Monticone and colleagues in a recent meta-analysis [12].

High dietary salt intake itself is associated with arterial hypertension as well as epithelial swelling, vascular stiffening, increased pulse pressure, left ventricular hypertrophy and albuminuria [61–63]. With the majority of these effects being blood pressure-related, evidence also suggests direct negative impact of dietary sodium. It has been shown that high salt diet increases angiotensin II type 1 (AT1) and decreases angiotensin II type 2 (AT2) receptors, thereby promoting vasoconstriction and cardiovascular damage [64, 65]. Counterintuitive to pathophysiological considerations increased activity of cardiac aldosterone synthase (CYP11B2) and finally higher cardiac aldosterone synthesis were reported under salt administration, findings which are controversially discussed [66–68]. However, this could further add insult to cardiac injury

under these circumstances. Another incompletely solved issue represents endogenous ouabain (EO) or ouabain-like compounds. These compounds were reported to be released in response to ACTH, angiotensin II and sodium administration and to be linked to aldosterone levels [58, 69, 70]. On the one hand, the secretion of EO is supposed to cause vasoconstriction and hypertension and thus could explain synergistic effects of aldosterone and high dietary salt intake. On the other hand, to date it is not even sure, if EO actually exists or not, as some research groups have been unable to detect EO in human circulation [58, 71, 72].

One alternative mechanism to explain the interaction of salt and aldosterone might be a high salt intake-mediated overexpression of transforming growth factor β 1 which is known to exert profibrotic actions [73].

Moreover, effects of salt intake on redox state are frequently reported. In general, oxidative stress is characterized by an imbalance between the generation of reactive oxygen species (ROS), oxygen-containing molecules with an unpaired electron, especially the superoxide anion O_2^- , and their detoxification by antioxidant systems such as superoxide dismutase and catalase. ROS are generated by normal respiration of cells and amongst others by xanthine oxidase and NADPH oxidase. 8-Isoprostane is one of the stable products generated under the impact of ROS and it is hence used as a marker of oxidative stress in vivo [74, 75]. In this context it has been shown that in salt-sensitive hypertension, high salt intake results in higher plasma concentrations of the lipid peroxidation product isoprostanes [76, 77]. In rats on a high salt diet it could further be shown that the renal expression of NAD(P)H oxidase is increased resulting in further oxidative stress [78].

Another link between oxidative stress and high dietary salt intake are the pro-inflammatory effects mediated by changes in gut microbiota [79, 80]. Animal as well as human studies could show gut dysbiosis in subjects suffering from hypertension [81, 82]. This is supposed to impact negatively on the intestinal mucosa and increase its permeability for pathogens, eventually promoting inflammation and oxidative stress [83, 84]. The relevance of the gut microbial composition was underlined by data from fecal microbiota transplant (FMT) studies where FMT from hypertensive rats to normotensive rats elevated blood pressure in the latter [85]. Toral and colleagues identified the pro-inflammatory interleukin 17, produced by T helper 17 (T_H 17) cells, to be essential for the FMT-induced blood pressure increase as well as the effects on endothelial dysfunction [85]. In this context, administration of a neutralizing antibody against IL-17 reduced blood pressure and improved endothelial dysfunction induced by FMT [85].

High dietary salt intake by itself has been shown to increase plasma levels of the pro-inflammatory cytokines IL-6 and IL-23 and to activate T_H 17 cells, resulting in inflammatory oxidative stress, respectively [79, 86]. Further it has been linked to gut dysbiosis favoring colonization by *Prevotella* and other species which are associated with elevated blood pressure and auto-inflammatory diseases as well as the depletion of *Lactobacillus spp.* [79, 87–91]. In line with these findings Wilck and colleagues could show that administration of *Lactobacillus murinus* protected mice from activation of T_H 17 cells and abrogated hypertension when challenged with a high salt diet [79]. Comparable with the results of the animal studies they could also show a reduction of *Lactobacillus spp.* as well as an increase in T_H 17 cells and blood pressure in humans on a high-

salt diet. Taking these findings into account the impact of salt intake on gut microbiota and consecutively T_H 17 mediated inflammation could be another mechanism of salt induced oxidative stress. Interestingly, aldosterone has also been reported to promote the T_H 17 pathway while spironolactone potentially blocks the activation of T_H 17 cells [92, 93].

Altogether there is accumulating evidence for high salt intake raising oxidative stress in animals as well as in humans. Under conditions of oxidative stress, the aldosterone-independent activation of the MR has received particular interest.

To better understand the consequences of an altered redox state it is important to recall that the classical effects of aldosterone are MR-dependent genomic effects on sodium excretion in the distal nephron of the kidney. In general, the MR has similar affinity for aldosterone and cortisol. As aldosterone accounts only for about 1 % of free steroids in epithelial tissues (e. g., kidney, colon, sweat and salivary gland) it is the enzyme 11 β -HSD2, which converts cortisol into its inactive metabolite cortisone, with parallel conversion of the cofactor NAD⁺ to NADH, thereby rendering aldosterone to the main activator of epithelial MR [44, 94, 95]. In other tissues, such as the heart, 11 β -HSD2 is not expressed at relevant levels, leading to cortisol as the primary ligand. Of note, cortisol under normal redox conditions is supposed to act as an MR antagonist [96, 97].

In the case of oxidative stress, Mihailidou and colleagues showed, using experimentally induced myocardial infarction in rodents as a trigger, that exogenous administration of cortisol as well as physiological levels of glucocorticoids both increase the infarct area. As this effect could not be blocked by the glucocorticoid/progesterone antagonist RU486 but only by spironolactone it seems that glucocorticoids can act as MR agonists in case of oxidative stress and hence increase cardiovascular damage [97]. The relevance of oxidative stress for these agonistic effects was further strengthened by Mihailidou as the administration of TEMPOL (4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl), a superoxide dismutase mimetic, also blocked the pro-apoptotic effects of aldosterone and cortisol [97]. These findings might provide a treatment rationale for patients suffering from PA: not only as aldosterone and salt excess increase oxidative stress by themselves but in addition because those patients frequently feature cortisol co-secretion [98, 99]. The latter aggravates cardiovascular damage in scenarios with both high and low oxidative stress as glucocorticoid excess impairs the conversion of cortisol to cortisone, leading to glucocorticoid-mediated mineralocorticoid effects even in 11 β -HSD2 protected epithelial tissues (► **Table 1**) [100–105]. As stated previously, changes in redox state may further aggravate glucocorticoid MR agonism. This is attributed to a loss of NADH which is supposed to act as a putative ligand specific co-repressor exclusively at glucocorticoid-occupied MR [96, 106–108].

Relevance of dietary salt intake for patients with PA following initiation of treatment

Besides the synergistic effects of salt and aldosterone excess, there is accumulating evidence from clinical studies that high salt intake plays an important role for cardiovascular risk even after successful treatment of PA. In a recent study it has been shown that lower dietary sodium intake, estimated by measuring 24-hour urinary sodium excretion, after treatment for PA correlated with a steeper

► **Table 1** Proposed effects of aldosterone, cortisol, and dietary salt intake on blood pressure and cardiovascular risk.

Aldosterone	Renin	DSI	Cortisol	BP/CV risk	Potential underlying cause
normal	normal	normal	normal	Normal	None
normal	low	high	normal	↑	High dietary salt intake
high	high	low	normal	↔	Secondary aldosteronism
high	low	high	normal	↑ ↑	PA
high	low	high	high	↑ ↑ (↑)	PA with cortisol co-secretion

BP: Blood pressure; CV: Cardiovascular; DSI: Dietary salt intake; PA: Primary aldosteronism.

decrease of left ventricular mass index (LVMI) [25]. This effect was independent of blood pressure and treatment modality. Pimenta and colleagues observed that proteinuria was significantly reduced after unilateral adrenalectomy for the treatment of PA while the positive correlations of proteinuria and salt intake persisted even after the procedure [26]. Since both LVMI and proteinuria are independent cardiovascular risk factors, a low sodium diet could improve target-organ protection even after successful treatment of PA.

Interestingly, in a post hoc analysis of 148 consecutive PA patients of the German Conn's Registry (66 with unilateral and 82 with bilateral PA) there was a significant reduction of dietary salt intake, as estimated by 24-hour urinary sodium excretion, after one as well as three-years of follow-up, in patients who had undergone unilateral adrenalectomy but not in those on MRA treatment [29]. However, this finding contrasts with data from Catena and colleagues who detected a decrease in salt intake in both treatment groups at one-year of follow-up. This discrepancy could be attributable to different treatment strategies in both cohorts with varying dosing of MRA and consecutively MR antagonism as well as the intensity of lifestyle intervention [29]. A decrease in salt intake after ADX constitutes an independent protective element favoring cardiovascular risk reduction in patients with unilateral PA who opt for surgery.

In this context, it is of interest that Hundemer and colleagues showed a strong correlation between plasma renin activity and cardiovascular outcome in PA patients undergoing MRA treatment [109]. In this study, 134 patients with suppressed plasma renin activity had a risk profile almost three times higher than patients with unsuppressed renin although the two groups did not differ in blood pressure levels. The authors attributed this increased risk to insufficient MRA treatment. As sodium intake was not recorded it can be speculated if it was not at least in part dietary sodium restriction which was associated with higher renin levels and could therefore act as a confounder for a more favorable cardiovascular outcome [110].

Conclusions

Huge evidence from experimental and clinical studies indicates that aldosterone excess inadequate for salt status is required to cause cardiovascular and cerebrovascular target organ damage in pa-

tients with PA. Here it should be kept in mind that the central effects of aldosterone increase salt appetite and thereby potentially counteract lifestyle interventions aimed at the reduction of dietary salt intake. Clinicians should, in addition to providing sufficient treatment of aldosterone excess in PA, not hesitate to encourage these patients to reduce their daily salt intake in order to minimize target organ damage, especially as usually after a few weeks of salt reduction the gustatory perception of salt is increased in general public which might help maintaining a lower dietary salt intake [111].

Further studies are required to collect more data about the effectiveness of strategies to reduce long-term dietary salt intake in PA and the impact of decreases in salt intake on cardiovascular risk, particularly after initiation of treatment for PA.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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