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COMMENTARY

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# Relationship between water and salt intake, osmolality, vasopressin, and aldosterone in the regulation of blood pressure

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## 1 | INTRODUCTION

Kanbay and Coll.[1] have reported a study showing that the acute effect of salt supplementation on blood pressure (BP) increase is dependent on plasma osmolality and that can be partially prevented by coadministration of water.

The regulation of plasma volume is complex and involves many factors interplaying each other, in particular the water-electrolyte balance, osmoreceptors, osmolality, vasopressin, the renin-angiotensin-aldosterone system (RAAS), prostaglandins, and natriuretic factors. The physiological equilibrium of these factors is able to keep BP within the normal range through the action of acute compensatory mechanisms. However, genetic/epigenetic and alimentary factors or organic diseases can affect the regulation of these factors leading to sodium and water unbalance or vascular reactions and developing hypertension.[2] For example, some people, as the African Americans, are predisposed to sodium retention showing low renin essential hypertension. Even the consumption of foods rich in soy or glutamate can be another cause of volume-dependent hypertension, as in Asiatic people.

The early management of predisposed subjects and the prevention of acquired factors are therefore necessary to avoid future cardiovascular risk.

## 2 | THE REGULATION OF SODIUM OSMOLALITY

Sodium is the principal electrolyte in human body, and its plasmatic concentrations are finely maintained in a narrow range despite great variations in water and salt intake. It is the principal constituent of serum osmolality, which is also dependent on water intake and on water and sodium excretion through urine and perspiration. In humans, osmolality is principally maintained between 280 and 295 mOsm/kg of water through an integration of thirst, vasopressin secretion, and renal responsiveness to vasopressin. Vasopressin, also called antidiuretic hormone, is synthesized in the hypothalamus in response to BP, volume, and osmotic changes in the plasma and in the cerebrospinal fluid. In particular, central osmoreceptors are sensitive to small changes in plasma osmolality and stimulate the neurons that secret vasopressin when osmolality increases. Vasopressin binds the receptors on renal collecting duct cells and promotes the reabsorption of solute-free water by stimulating insertion of the channel aquaporins into the membranes of renal tubules, leading to a decrease in plasma osmolality and an increase in urinary osmolality. Another potent stimulus of vasopressin is nausea and vomiting, both controlled by brain areas linked to the hypothalamus.

Serum copeptin is derived from the cleavage of the precursor of arginine vasopressin, and it is used as a surrogate marker of vasopressin, since it correlates with plasma levels of vasopressin and it is a stable molecule and easy to measure. Several studies have evidenced increased levels of copeptin in different pathological conditions, such as metabolic syndrome, chronic kidney disease, and hypertension.[3] In particular, copeptin levels have been associated with office BP and ambulatory BP, resistant hypertension, and essential hypertension in adolescents,[4] suggesting a certain role in arterial hypertension. Various mechanisms are thought to be involved, such as the local tissue RAAS activation in hypothalamus that stimulates vasopressin secretion, or an enhanced vasoconstriction,[4] or an increased tubular sodium retention.[5] More research is needed to evaluate the complex relationship between copeptin, RAAS, and hypertension.

  

## 3 | THE ROLE OF RAAS IN SODIUM CONTENT, HYPERTENSION, AND CARDIOVASCULAR RISK

The study of Kanbay and Coll[1] did not consider the aldosterone values and its effector mechanisms that are involved in the regulation of BP and volume. Salt intake and RAAS activation are regulated in an inverse fashion. The juxtaglomerular apparatus and the macula densa of kidney are sensitive to plasma volume and sodium, leading to renin secretion in case of decrease in renal perfusion pressure or in sodium concentrations or both. On the contrary, an increase in the salt concentration suppresses the RAAS and this mechanism can be independent from BP changes. Despite its fundamental role for body fluid balance, the salt-dependent regulation of the RAAS is still not completely understood.[6]

Aldosterone is regulated not only by the RAAS, but also by the potassium concentration and acutely by ACTH.[7] Aldosterone is interplaying with serum sodium and potassium levels, which are also regulated by osmolality and vasopressin.

In primary aldosteronism (PA), these mechanisms are altered being aldosterone secretion autonomous and independent from the volume. However, even in PA some compensatory mechanisms are activated, as the escape of kidney to the action of aldosterone with polyuria and sodium excretion.[8] These effects are mediated by an increase in natriuretic peptides and by down-regulation of mineralocorticoid receptors (MRs).[9] The consequence is the establishment of a new equilibrium of all the factors blocking a further increase in sodium and water reabsorption.

It is well known that aldosterone has another important effect beyond the regulation of water-electrolyte balance: it shows a proinflammatory action, responsible for the profibrotic effects associated with cardiovascular risk.[10] It is worthy of note that inflammation and cardiovascular complications are also present in secondary aldosteronism, independently from the increase in BP or sodium. From these observations, it seems that sodium and hypertension are not strictly necessary for induction of aldosterone-related profibrotic effects, while they are primarily involved in the increase in BP. The inflammatory effect of aldosterone is related to the presence of MR in the inflammatory tissues and, in particular, in macrophages and lymphocytes bearing their MR and mediating both genomic and nongenomic effects.[11] The studies of Pitt[12,13] have clearly evidenced that MR blockers are able to reduce the cardiovascular risk. These studies, however, emphasize that the decrease in plasma volume, sodium, and BP plays an additive role in the prevention of cardiovascular risk.

## 4 | THE RELATIONSHIP BETWEEN SODIUM AND HYPERTENSION

Dietary salt excess is a major cause correlated with the rise in the BP with age, and hypertension is virtually absent in populations with an individual salt intake lower than 50 mmol/d.[14] However, the pathogenetic mechanisms are not completely understood. Previous studies have demonstrated in both normotensive and hypertensive participants that a large and sudden increase in salt intake usually causes a 2 to 4 mmol/L rise in plasma sodium, leading to an increase in osmolality that may have a direct pressor effect.[15] Moreover, it has been shown that each gram of moderate additional salt intake leads to a BP increase of approximately 1 mm Hg[6] and a 6 g salt ingestion is associated with an increase in sodium levels, serum osmolality, and BP values.[16]

The study of Kanbay and Coll[1] reports an increase in BP in all the evaluated groups in the first 2 hours after the starting of the different protocols, but this difference remained significant at 3 and 4 hours only in the group that received the lentil soup with 3 g of salt. This group showed a similar pattern of changes even in plasma osmolality, sodium, and copeptin during the visits. On the contrary, in the groups receiving salty soup with water, the changes in plasma osmolality, sodium, and BP were prevented.

From these results, some considerations can be drawn. An intake of sodium alone produces an immediate effect on BP, serum osmolality, sodium, and copeptin, hypothesizing a predominant direct role of sodium and osmolality increase in the rise of BP, probably mediated by a central mechanism rather than to volume expansion. In the first 2 hours, the RAAS is probably not suppressed contributing to the increase in BP. After 2 hours, some compensatory mechanisms, such as water retention and volume expansion, develop with a decrease in all parameters, as evidenced in all the groups. In particular, the ingestion of water, at the time of salt intake, allowed a lower increase in serum osmolality, sodium, and BP levels compared with only salt intake at each time point. The concurrent water intake can induce a prompt dilution of sodium and a volume expansion, finally suppressing the RAAS and normalizing sodium and osmolality. It is worthy of note that among confirmatory procedures for PA, the volume expansion with saline test is done by measuring aldosterone after 4 hours of saline infusion or after 3 days of oral salt loading,[17] confirming that this reaction needs more time to be clearly expressed.

In conclusion, future studies should investigate the effects of prolonged water and sodium administration on changes in BP, RAAS, and copeptin in animal models, even considering the different genetic predisposition to salt sensitivity.

## CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

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