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PRO/CON DEBATE

Sodium—not harmful?

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Abstract

Background The temporality between the mandated reduction of salt in processed food and the decrease of death from stroke and ischemic heart disease, the association of hypertension, and cardiovascular disease led many public health organizations to recommend reducing dietary sodium to a maximum of 2300 mg per day. It turns out that some nuances can be brought about to this universally shared belief.

Methods & Results Indeed, consideration of health outcomes instead of only blood pressure as a surrogate marker of cardiovascular disease and prognosis gave contradictory results whereas low sodium intake is associated to an excess of death and cardiovascular events.

Conclusions Accordingly, sodium intake should be adapted to individual risk factors, and evidence is still clearly lacking to support indiscriminate recommendations in healthy people. By contrast, a restricted sodium diet is certainly useful in patients with chronic kidney disease exposed to salt retention, and by reciprocity, low sodium diet must be absolutely avoided in all patients presenting renal or extra renal sodium wasting where sodium depletion is a life-threatening condition.

Keywords Cardiovascular disease · Blood pressure · Table salt · Dietary · Heath outcomes

Sodium intake is doubly vital for mammals and human life. Indeed, the total amount of sodium in the system is determining the volume of the extracellular fluid (Fig. 1a) and the quality of organ perfusion [1, 2]. In addition, changes in the sodium potassium gradient between the extracellular and the intracellular fluids are also mandatory for the depolarizaton then the repolarization of all excitable cells, including neurons and cardiomyocytes [3]. Consistently, herbivorous domestic mammals need salt supplementation to be bred in good conditions [4] and herbivorous wild mammals have a natural avidity for salt and mineral sources [5]. In humans, who are also mammals, the mean sodium intake is 3.6 g/day, and for 90% of persons, the variability of sodium intake holds in a very short range from 3.1 to 4.4 g/day (meaning 8 to 11 g/day of table salt) [6]. Of note, the mean intake value of 3.6 g per day coincides with an inflection point at which lower intakes have been reported to elevate plasma renin activity [6]. Sodium appetite and subsequently sodium intake are closely regulated by neurons expressing angiotensin-2 and aldosterone receptors located in the third ventricle and can explain the worldwide range of spontaneous sodium intake [6]. Interestingly, this regulation can be influenced by the sodium intake while preference of sodium chloride-rich foods in adults coincides with infants' exposure to salty foods. It implies that a change in adult behavior is accessible to early education [7].

Salt retention is associated to a steady expansion of the extracellular fluid and a subsequent hypertension [1], in order to maintain the homeostatic value of osmotic pressure to 294 mosmol/kg of water (Fig. 1b) [8]. In apes, the increase of daily salt intake in non-human primates over the natural level during 2 years progressively leads to hypertension although a full reversibility has been observed when the natural low sodium vegetarian diet was resumed [9]. In humans, hypertension has been clearly linked to several genes involved in the sodium balance and especially in the renal sodium reabsorption and its regulation [10]. For decades, the progression of chronic kidney disease and the development of cardiovascular damage as well as premature death have been closely associated to hypertension [11–13]. Patients with chronic kidney disease that are prone to develop salt retention consistently encounter a high

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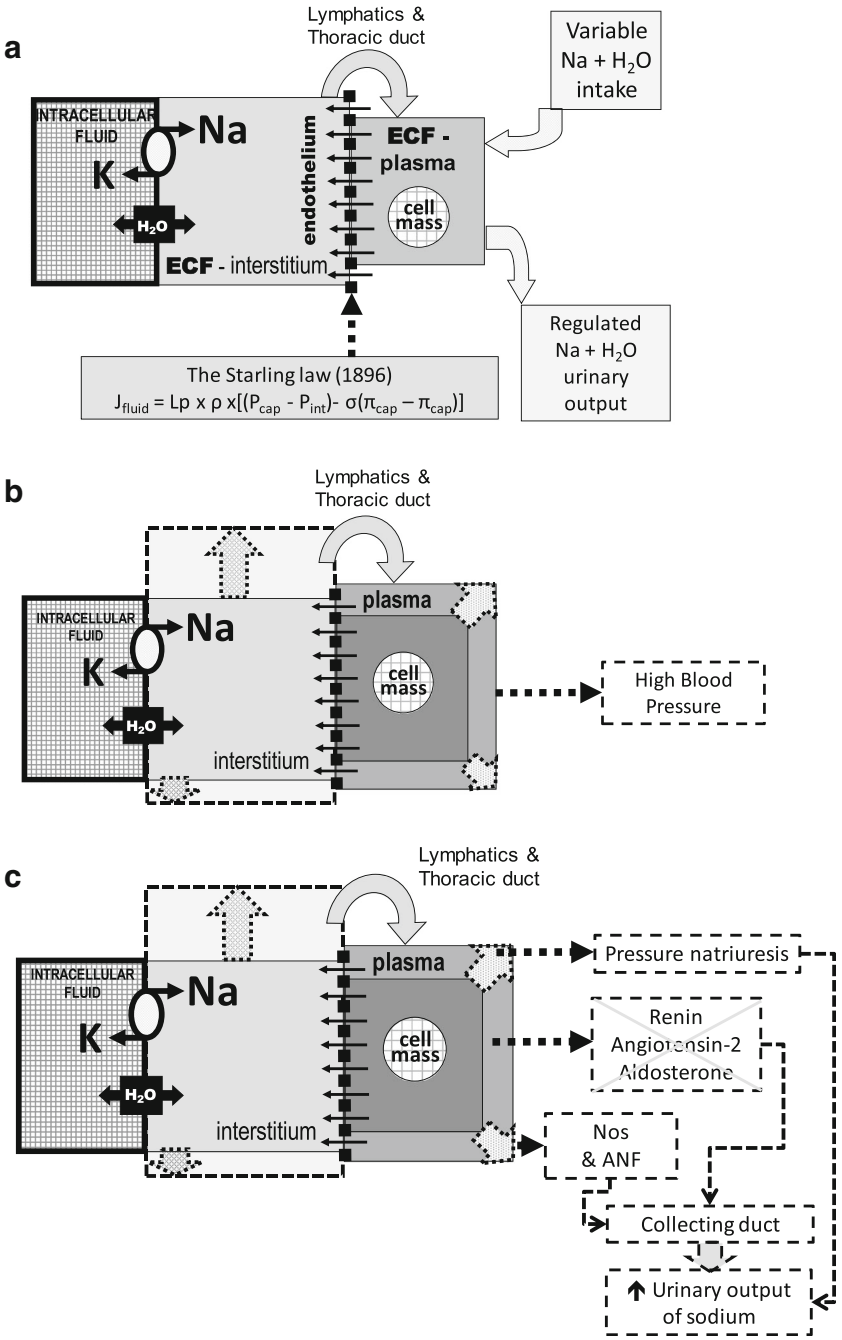

risk of hypertension, and cardiovascular events while the prevalence of heart failure are proportional to sodium intake [12]. Those facts led to promote public health policies aiming to reduce the daily sodium intake through a better control of sodium content, especially in processed food [14]. It recently turned out that some nuances might be brought about to this universally shared belief. Indeed, consideration of health outcomes instead of only blood pressure as a surrogate marker of cardiovascular disease gave contradictory results in several observational studies among the general population [15–20].

Sodium balance

Every day, the balance of the extracellular fluid is challenged by uncontrolled intakes of sodium and water that are compensated by adapted urinary outputs. The total amount of sodium is tightly regulated in the kidney by the regulation of sodium reabsorption in the collecting duct (Fig. 1c). At steady state, the ultimate concentration of sodium in the final urine is controlled by the level of circulating aldosterone and angiotensin-2, itself fixed by the level of the blood pressure through the

◀ **Fig. 1** **a** Physiology of fluids. Water is the solvent of the intracellular and the extracellular fluids. The intracellular fluid is made of 10,000 billions of cells separated by plasma membranes. By contrast, the extracellular fluid is made of the interstitium and the plasma volume that are separated by the capillary walls. The pressure regimen between plasma and interstitium leads to a permanent fluid transfer toward the interstitum according to the Starling law. The daily volume of filtration is recycled in the plasma through the thoracic duct and the peripheral veins of lymphatic nodes. The extracellular fluid is a saline solution of sodium while the main cation in the intracellular fluid is potassium due to the expression of the sodium pump at the surface of every cell of the system. Aquaporines expressed at the surface of all cells allow water transfer and equal osmotic pressure in both fluids. The osmotic pressure in the extracellular fluid is tightly regulated at a steady state of 296 momol/kg (range 284–304) by the thirst and the hormonal regulation of renal water output. The volume of the extracellular fluid is subsequently determined by a steadily total amount of sodium in the system despite the daily challenge of unbalanced water and sodium intakes. **b** Physiology of sodium retention. Sodium retention is due to the impairment of the regulation of renal sodium excretion and subsequently leads to an expansion of the extracellular fluid volume in order to maintain a steady nominal osmotic pressure in the system. The steady expansion of the plasma volume leads to an increase of the blood pressure. Noteworthy, the genetic background of hypertension is closely linked to genes involved in the mechanisms of renal sodium reabsorption and its regulation. **c** Physiology of a sodium load. In healthy people, a sodium load does not mean sodium retention. The diffusion of a sodium load in the extracellular fluid leads to an expansion of the extracellular fluid to maintain the level of the osmotic pressure. The subsequent plasma volume expansion is increasing the blood pressure, inhibiting the release of renin, and decreasing circulating angiotensin-2 and aldosterone. It leads to a modulation of the sodium reabsorption in the collecting duct and allows buffering the effect of a standard sodium intake. In case of a dramatic and massive load of sodium, the mechanism is completed by the atrial natriuretic factor that triggers a profound natriuresis and diuresis. The tubular mechanism of pressure natriuresis mainly involves the proximal tubule but is not fully elucidated

secretion of renin in the arteries of the juxtaglomerular apparatus [21]. In case of sodium depletion, the human kidneys are able to retain all the sodium that is filtrated every day due to a powerful reabsorption in the collecting duct that can, on demand, decrease the sodium concentration in the final urine down to a zero level [21, 22]. It suggests that humans are able to survive despite steadily sodium deprivation [23], but it does not mean that sodium deprivation is harmless. In healthy humans, a standard sodium intake is consequently balanced by the modulation of sodium reabsorption (Fig. 1c) that prevents any sodium retention. In case of a dramatic and massive load of sodium, the tension of the right atrium wall leads to the release of the atrial natriuretic factor (ANF). ANF triggers a profound natriuresis and diuresis by a series of concerted actions along the nephron, including stimulation of glomerular filtration and inhibition of net salt and water reabsorption in the cortical and inner medullary collecting ducts [24]. Last but not least, increments in water and sodium excretion in response to an increase in perfusion pressure in the renal artery have been recognized more than a century ago using a model of isolated perfused kidneys [25]. Altogether, those mechanisms allow preventing the dangerous effects of acute hypervolemia, such as life-threatening levels of hypertension and pulmonary edema. In addition to the tight renal regulation of the sodium balance, the storage of sodium in collagen, glycosaminoglycans, and some subsets of immune cells without proportional water retention allows to buffer sodium loads in excess whereas the volume of the extracellular fluid remains stable [26]. Consequently, in healthy people, a standard sodium diet does not necessarily mean sodium retention but salt sensitivity may vary among populations and many healthy people may show more hypertensive effect from sodium intake than others (Table 1) [27, 28].

Blood pressure and dietary sodium

A subset of 1499 patients originating in the addition of 1109 from the FLAMENGHO study (Flemish Study on Environment, Genes, and Health Outcomes, 1985–1990) to 390 from the EPOGH cohort (European Project on Genes in Hypertension, 1999–2001) had BP and sodium excretion measured at baseline and last follow-up (2005–2008) on a yearly basis [29]. Each 100-mmol increase in the sodium diet was associated to an increase of only 1.71 mmHg (+ 1.5% of the base level) of systolic blood pressure and no significant changes in diastolic blood pressure [29]. Although the study confirmed that a doubling of sodium intake was associated with a mild increase (2.2%) of systolic blood pressure, it failed to find a significant change in diastolic blood pressure despite the large size of the population. In addition, the longitudinal analysis of systolic blood pressure during 6 years showed a yearly increase of 0.37 mmHg for systolic blood pressure and 0.47 for diastolic blood pressure, whereas sodium excretion did not change or slightly decreased. Those results suggest that blood pressure and sodium intake might not be necessarily related on the long term, at least in a European population of mid age [29]. One should regret that the variability of salt sensitivity has not been assessed in this study.

A meta-analysis of 167 studies reciprocally showed that a low sodium diet led to a decrease in systolic and diastolic blood pressure whatever the initial level of blood pressure and the ethnicity [27]. Of note, the negative gain of blood pressure is homogeneous and moderate in normotensive individuals (Table 1), limited to less than 4% of the normal values of systolic and diastolic blood pressure [27]. By contrast, in hypertensive patients, the negative gain is variable according to ethnicities, low sodium diet being the most efficient on systolic blood pressure in Asians (− 10%) and Africans (− 6.5%) compared to Caucasian (− 5%) [27]. Altogether, those results indicate an increased salt sensitivity in hypertensive patients and a clear variability of salt sensitivity in normal individuals.

Table 1 Differential of blood pressure in mmHg under low sodium diet (data extracted from [27]. Results are given in median and interquartile range

Individuals	Blood pressure	Differential value in Caucasians	Differential value in Asians	Differential value in Africans
Normotensive	Systolic	− 1.27 *(− 1.88–0.66)*	− 1.27 *(− 3.07, − 0.54)*	− 4.02 *(− 7.37, − 0.68)*
	Diastolic	− 0.05 *(− 0.51, + 0.42)*	− 1.68 *(− 3.29, − 0.66)*	− 2.01 *(− 4.37, + 0.35)*
Hypertensive	Systolic	− 5.48 *(− 6.53, − 4.43)*	− 10.21 *(− 16.98, − 3.44)*	− 6.44 *(− 8.85, − 4.03)*
	Diastolic	− 2.75 *(− 3.34, − 2.17)*	− 2.68 *(− 4.03, − 1.16)*	− 2.40 *(− 4.68, − 0.12)*

Epidemiological facts

The NHANES I study (National Health and Nutrition Examination Survey) gathering 11,346 individuals examined the linkage of sodium intake to morbidity and mortality [15]. The population of the study was shared in four quartiles according to the level of sodium intake based on a nutrition investigation by a 24-h recall. Although less reliable than 24-h urine sodium excretion to assess sodium intake, the level of blood pressure was identical whatever the level of the sodium intake. Unexpectedly, the death rate was lower in the highest quartile compared to the lowest quartile of sodium intake suggesting that harm may outweigh the supposed benefits of a low sodium diet [15]. However, people in quartiles were not equal in terms of initial morbidity: a history of either cardiovascular disease or hypertension was more prevalent in the lower quartile of sodium intake compared to the upper quartile. However, authors mentioned that the results were similar in a sub-analysis restricted to participants with no reported history of CVD at baseline. Moreover, a work done in 2807 patients with diabetes type 1 confirmed that the progression to end-stage renal disease and the death rate was higher in the patients undergoing a very low sodium intake compared to others [30]. Indeed, a modelization of the relative hazard ratio according to the level of sodium intake showed a similar risk at 50 and 270 mmol/day [30].

The aforementioned European study [29], including people without history of cardiovascular disease and treated hypertension, was based on the measurement of the 24-h urinary sodium output considered as a surrogate for the daily sodium intake. While people in the highest tertile of sodium intake had a higher incidence of hypertension during the follow-up, they had the lowest rate of cardiovascular events and mortality [29]. The NHANES III study was also done on 8699 individuals without initial cardiovascular history. Sodium intake was assessed on a 24-h diet recall. It showed similar results in terms of cardiovascular death, confirming the unexpected harm of low sodium diet [16]. A refined analysis of this population showed that the protection from cardiovascular mortality was proportional to the potassium intake instead to be related with the sodium intake [31]. Consistently, higher sodium-potassium ratio hit the highest risk of cardiovascular mortality while addition of sodium to processed foods obviously contributed to this undesirable ratio. At last, the Worksite Hypertension Study found no significant association between 24-h urinary sodium excretion and cardiovascular outcomes in the range from 55 to 225 mmol/day of sodium (3.5 to 13 g/day of salt). By contrast, a significant association of low sodium diet to all-cause mortality was evidenced [32]. Altogether, these findings suggest that sodium may be less dangerous than expected and the relationship with cardiovascular mortality being doubtful. Indeed, consistently with a U-shaped association between sodium intake and health outcomes, a range from 2.645 to 4.945 g/day of sodium has been associated with the most favorable health outcomes, within which a variation in sodium intake is not associated with variation in mortality [33]. It turns out that this range is somehow the mean spontaneous intake of 90% of people worldwide [22].

Animal experiments

Rats undergoing an extremely low salt diet (equivalent to less than 100 mg/day of Na Cl in humans) develop left ventricular hypertrophy and increased interventricular septal thickness while shortening fraction of the left ventricule remains unchanged [34]. Heart fibrosis and increased myocyte diameter were evidenced at the histological level. Those damages of the heart were consistently associated to the activation of plasma renin-angiotensin-aldosterone, sympatho-adrenal systems and activation of cardiac prorenin as well as angiotensin-2 AT1 receptor and their downstream signals [34]. Noteworthy, high sodium intake suppresses aldosterone and angiotensin-2 pathways through the activation of the nitric oxide synthase within the collecting duct leading to a down-expression of the epithelium sodium channel (ENaC) and the sodium pump [35]. In addition, the high sodium diet also leads to a down expression of ENaC in endothelial cells favoring vasodilation [36]. One should recall at this stage that longevity associated variants (DNA polymorphisms associated to individual surviving to the one percentile of age) include genes involved in the regulation of endothelial NO synthase [37]. One should remind that biological systems remain complex realities that cannot be analyzed according to one single concept.

The salt debate

The 2011 AHA (American heart Association) presidential advisory on sodium reduction recommends a sodium intake below 2300 mg/day (5.8 g/day of NaCl) in the general population and below 1500 mg (3.8 g/day of NaCl) in African Americans, healthy individuals over 51 years of age and patients with hypertension, diabetes, and chronic kidney disease [38]. The list of AHA arguments effectively deserves consideration: a lack of causal evidence between low sodium diet and increase mortality, methodological flaws in estimating sodium intake resulting in inconsistency of results relating the reduction of sodium intake and cardiovascular mortality, the temporality between the legally enforced reduction of salt in processed food and the decrease of death from stroke and ischemic heart disease in the United Kingdom, the strong association of hypertension with the risk of cardiovascular disease [38–40]. On the other hand, several "sodium dissident" authors deny the sodium reduction health policy in the US on another list of arguments that also deserve consideration: data from basic science on the activation of the renin-angiotensin system, the threshold of sodium intake that activates the renin angiotensin system, the universality of the spontaneous level of sodium intake in general populations, and measures of global health outcomes according to the level of sodium intake [17, 19, 20, 41]. The main issue of controversy is the method to measure sodium intake while 24-h diet recall and estimation of the 24-h urinary sodium excretion on a morning sample of urine are directly accused of significant bias [39, 42]. Randomized control trials on long lasting period of time come up against the poor adherence to sodium diet and individual "random" behavior changes during the time of the study. While adherence to 1800 to 2300 mg/day level of sodium has proven difficult in a general population with free access to any food, a group gathering "orthodox and dissident" authors arrived at a consensus that a clinical trial in a prison population (particularly federal prisons in the USA) might provide the best setting to conduct the trial [43]. According to authors themselves, many issues have to be considered before moving forward in this direction.

Conclusion

Humans like all living beings are not created equal and sodium intake should be adapted to individual risk factors. There is nothing obvious to support a general rule applying for the general population and a sodium intake in the spontaneous range might not be harmful in most people. Consequently, evidence is still clearly lacking to support indiscriminate recommendations in healthy people. By contrast, a restricted sodium diet is certainly useful in patients with chronic kidney disease exposed to salt retention while obviously by reciprocity, low sodium diet has to be avoided in all patients presenting renal or extra renal sodium wasting where sodium depletion may be life-threatening.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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