Cholesterol

Another Salty Pathway to Cardiovascular Disease?

Carmine Zoccali, Francesca Mallamaci

The ability to maintain water balance, a function regulated by the antidiuretic and vasoconstrictor hormone arginine vasopressin, is a fundamental physiological function.[1] Vasopressin levels are tightly associated with plasma osmolality, a parameter that mainly depends on sodium levels in biological fluids. High osmolality triggers arginine vasopressin release, which in turn reduces water clearance by the kidney and corrects hyperosmolality/hypernatriemia. The concept that plasma sodium regulation depends mainly on water balance rather than on sodium balance is a centerpiece for the interpretation of electrolytes disturbances,[2] and it is commonly held that salt intake raises blood pressure (BP) almost exclusively by expanding the extracellular volume, that is, by the water-reclaiming effect of sodium. However, sodium intake per se has a measurable influence on serum sodium and on BP.[3] Hypertensive subjects have a limited renal ability to excrete sodium and a parallel limited ability to retain the same cation in osmotically inactive form in the skin and in other tissues. The inability to buffer sodium in nonosmotic form in the skin and in other tissues constitutes an additional relevant mechanism, whereby sodium raises BP.[4] In the skin, macrophages are a critical cell species for the response to interstitial hypertonicity by high sodium.[5] Sodium is per se implicated in hypertension and in a variety of cardiovascular alterations, including left ventricular hypertrophy, arterial rigidity, high peripheral vascular resistance, and nitric oxide–dependent endothelial dysfunction.[6] In this pathophysiological scenario, it comes as no surprise that subtle increases in serum sodium just above the upper limit of the normal range predicted an excessive risk for stroke and coronary artery disease events in at least 2, large community-based studies.[7,8]

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The bench to bedside approach is central to patient-oriented research. However, more often than not, progress in science is not unidirectional, and the palindromic journey leading to discovery may start at the beside rather than at the bench. In the case of Gao et al,[9] article published in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, the starting point is the association between serum sodium and cardiovascular risk noted in the abovementioned epidemiological studies.[7,8] A possible explanation for this phenomenon is that, also beyond BP, sodium per se may materially influence the level of classical risk factors. Gao et al now present exploratory analyses testing within-normal-range variations in serum sodium and parallel variations in cardiovascular risk factors in the frame of a robust cardiovascular epidemiology study, such as the ARIC study (Atherosclerosis Risk in Communities).

Cross-sectional studies are at the bottom (just above case reports) of the ladder of evidence aimed at defining disease etiology.[10] This limitation depends on the fact that this design has no time dimension, and therefore, for associations detected in such studies we cannot decide which is the cause and which is the effect. Yet, the cross-sectional study is of unquestionable value for generating interpretative clues to be tested in higher level studies, namely longitudinal studies and clinical trials.

Gao et al made major efforts for mitigating the limitations of the cross-sectional design. First, they interrogated a large database (ARIC, see above) and eliminated the possible confounding effect of the use of cholesterol-lowering or antihypertensive drugs and bravely focused on individuals who had a serum sodium within normal range (135–145 mmol/L) range. The selected ARIC population was large (n=8617), and the sodium–cholesterol relationship was tested in various strata (males/females, black/white, smoker versus nonsmoker) and confounding by other known risk factors, including glucose, insulin, body mass index, waist to hip ratio, and calorie intake, and renal function (glomerular filtration rate) was controlled for by state of art multiple regression analysis. Overall, the analysis revealed a direct association between sodium and total cholesterol and other lipid parameters and confirmed the association between serum sodium and systolic and diastolic BP registered in previous clinical studies.[3] Of note, the increases in lipid parameters and in BP brought by increasing levels of serum sodium (10 mmol/L) were of apparent clinical relevance because the same increases were equivalent to those associated with an age difference of ≈7 to 10 years. A merit of this hypothesis-generating study is that it included an in vitro experiment, showing that high sodium promotes lipid accumulation in cultured adipocytes. In this experiment, an increase in sodium from the low end (135 mmol/L) to the upper end (145 mmol/L) of the normal range of serum sodium produced a remarkable increase (≈30%) in lipid content in adipocytes, which was entirely attributable to the osmotic effect of this cation. Because sodium is an extracellular cation, high levels of this electrolyte trigger osmotic efflux of water from cells, thereby reducing cell volume and increasing intracellular tonicity alongside. As discussed by Gao et al, among the cellular responses to hypertonicity, the increase in

From the CNR-IFC, Clinical Epidemiology and Pathophysiology of Hypertension and Renal Diseases, Ospedali Riuniti, Reggio Calabria, Italy (C.Z., F.M.); and Nephrology, Hypertension and Renal Transplantation Unit, Ospedali Riuniti Reggio Calabria, Italy (F.M.).

Correspondence to Carmine Zoccali, FASN, FNKF, FERA, CNR National Research Council (Italy) Ospedali Riuniti, 89124 Reggio Calabria, Italy. E-mail carmine.zoccali@tin.it

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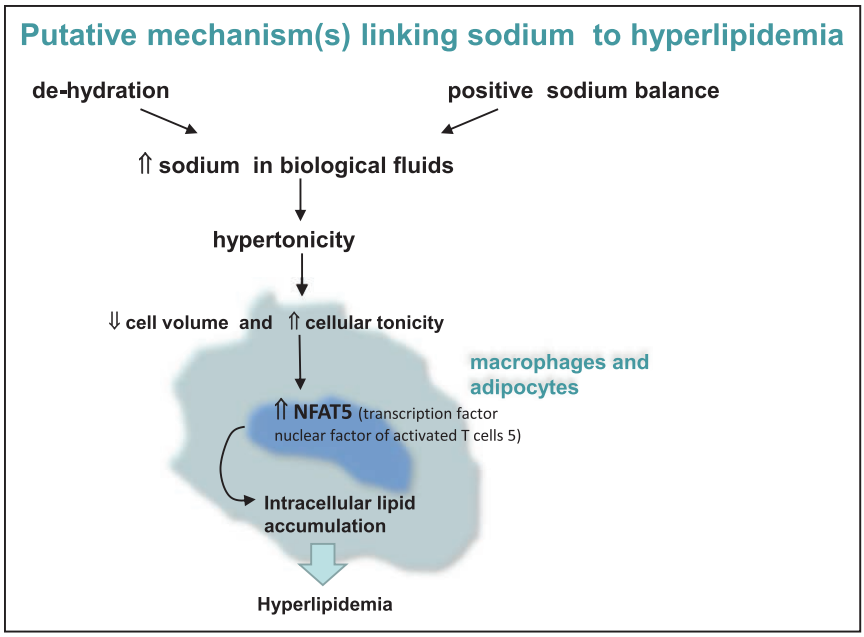

Figure. Putative mechanism whereby high serum sodium may cause hyperlipidemia. As discussed in the main text, conditions associated to relative dehydration or net sodium gain may increase serum sodium. This phenomenon raises the tonicity of biological fluids and reclaims water from cells. The cell volume shrinks and the intracellular tonicity increases. Cell hypertonicity in critical cell-species like macrophages and adipocytes is accompanied by the activation of the transcription factor NFAT5 (nuclear factor of activated T cells 5), a key element in the cell response to dehydration. NFAT5 in turn may hypothetically mediate lipid accumulation. In a model of NFAT5 gene haploinsufficiency, a marked attenuation in atherosclerosis occurs in the Apo-e (–/–) mice submitted to high fat diets.[12] Until now, the precise cellular mechanism(s) responsible for lipid accumulation by NFAT5 remain unknown.

the transcription factor NFAT5 (nuclear factor of activated T cells 5)[11] may be of peculiar relevance for lipid accumulation in adipocytes and macrophages. NFAT5 haploinsufficient (+/–) Apoe (–/–) mice given high-fat diet display much lower levels of atherosclerosis compared with the NFAT5 (+/+) Apoe (–/–) mice, but mechanism(s) underlying this phenomenon remain largely unknown (Figure).[12] As alluded to before, macrophages in the skin are critical for the response to interstitial hypertonicity by high sodium. Indeed, these cells release vascular endothelial growth factor, a vasodilator compound that promotes the growth of lymphatic vessels and mitigates the prohypertensive effects of high sodium.[5] Adipocytes have substantial biological similarities with macrophages,[13] and the hypothetical hypertonicity-induced lipid accumulation by NFAT5 may be another facet of the relevance of sodium buffering in the skin as a mechanism protective from the effects of excessive sodium levels.[4] Overall, this nice hypothesis-generating study by Gao et al opens interesting perspectives for countering the adverse effects of high sodium on human health. Whether lowering serum sodium by leveraging water and salt intake may translate into a reduction in serum cholesterol is a question of obvious relevance and warrants new investigations in appropriately designed clinical studies.

Disclosures

None.

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