There Is More to Salt Than Just a Pinch of Sodium

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See related article, pp 836–843

Water-Electrolyte Balance in Blood Pressure Homeostasis

Much of what human life is about is water (60% of body mass) and a handful of solutes. Of the latter, main cations include sodium, potassium, calcium, and magnesium, and the anions include chloride, bicarbonate, phosphate and organic anions, and proteins. The concentrations of sodium (135–145 mmol/L) and chloride (95–106 mmol/L) predominate in serum and constitute the bulk of serum’s osmolarity. In the course of evolution, complex regulatory mechanisms developed to keep the osmolarity (=280 mosm/L) and thus amount of water at desired level. With it came the role of main solutes and their regulatory mechanisms (i.e., renin–angiotensin–aldosterone system [RAAS]) in the regulation of blood pressure. Numerous studies demonstrated the role of sodium-based mechanisms in water homeostasis and blood pressure regulation. Recently, several well-designed studies showed that the level of ingested sodium correlated with the level of blood pressure or cardiovascular risk, and that the relationship is likely to assume a J-curve shape in population of patients with cardiovascular involvement or diabetes mellitus.1

Studies Documenting Importance of Chloride

However, experimental studies performed over several decades pointed to the possibility that the form of ingested or infused sodium is of importance. Both in animal models and in human studies, Kurtz and Morris2 and then Luft et al3 were among those who showed that blood pressure elevated when sodium chloride was ingested or infused, but not when the salt used was sodium bicarbonate or sodium citrate. These and other similar studies led to the consideration of chloride as a possible factor in the regulation of blood pressure.

Paradoxically, different picture arose when researchers related the concentration of chloride in serum to cardiovascular outcome. The major population-based study to investigate that was Belgian Interuniversity Research on Nutrition and Health. The main finding of this study was that the level of chloride ≤100 mmol/L as compared with higher levels was independently related to all-cause, cardiovascular, and noncardiovascular mortality.4 In the current issue of Hypertension, McCallum et al5 provide a robust confirmation of findings of De Bacquer et al, this time in treated patients with hypertension. The authors analyzed data of 12968 patients with hypertension followed up at the Glasgow Blood Pressure Clinic. The accumulated follow-up amounted to 197 101 person-years. They found that patients in the lowest quintile of serum Cl− (<100 mmol/L), compared with all other patients, had a 20% higher mortality (all-cause, cardiovascular, and noncardiovascular). A 1-mmol/L increase in serum Cl− was associated with a 1.5% (hazard ratio, 0.985; 95% confidence interval, 0.98–0.99) reduction in all-cause mortality. However, the level of chloride was not longitudinally associated with the level of blood pressure. The relationships were independent of sodium, potassium, and bicarbonate levels and blood pressure values, and they held after adjustment for treatment with diuretics and when adjustment for free water changes was made.5

Several important implications, as justly pointed by the authors, arise from their findings, including more attention to be payed to the levels of chloride, proposal to shift the lower limit of normal values from 95 to 100 mmol/L, and the need of more research in the field. The latter should include studies of nonfatal outcome, and mechanistic research, for currently, the explanations of the presented findings lack solid footing.

Putative Pathophysiologic Background

Attempts to hypothesize the pathophysiologic background for the relation between low chloride and mortality must include the physiological role of chloride currents and interaction of chloride with the osmolarity/volume homeostatic mechanisms. The compartmentalization of fluid and the gradients of solute concentrations across cell membrane and within the cell itself are the basis of the electric phenomena indispensable to the functioning of a biological entity. Most of the physiologically important ion currents are based on cation movements across membranes. However, a growing body of evidence supports the existence and relative importance of anionic currents, based on the Cl− transmembrane fluxes.6 The chloride channels have been found in cells of varied provenience and are thought to be important in processes ranging from maintenance of cell volume, apoptosis, secretion of insulin, and neuronal excitability through propagation of atherosclerosis (foam cell formation, formation of neointima in carotid arteries, and hypertension-related remodeling of cerebral arteries), ischemia/reperfusion injury, and vascular inflammation.6,7 Of note is the role of chloride currents in the regulation of sodium/water homeostasis.8 Aldosterone increases reabsorption of sodium by increasing the expression of sodium/chloride cotransporter in the luminal membranes of cells lining collective ducts, and low chloride was found to act on the

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macula densa to activate RAAS and thus lead to sodium conservation. Of the currently known several subtypes of chloride channels, 3 stand out, namely the phosphokinase-A–related chloride channel, stretch-activated chloride channel (similar or identical to the product of ClC-3 gene), and calcium-dependent chloride channel. These channels were found, with highly varied distribution and density, in most studied species and in most types of cells to be found in the heart, including the sinoatrial node, His-Purkinje system, and atrial and ventricular myocytes. Of these channels, the stretch-activated chloride channel/ClC-3 channels, which are activated by stretching of cell membrane at times when cell volume increases, seem to be of pivotal role in the chloride-related pathlogy. The back-translation of the results of McCallum et al to their possible pathophysiologic background is not easy, as at present, we are lacking studies directly answering the question of the link between low sodium and increased cardiovascular mortality. The picture that emerges from the research published thus far is that low serum chloride, whether associated with hypoopsmotic state or not, may facilitate the chloride currents, acting as an enhancer to the phenomena that have been traced as possible triggers increasing the probability of an open state of these channels. Such phenomena include ischemia-induced local hypoopsmotic state leading, in turn, to swelling of the cell and stimulation by tumor necrosis factor, leading to the increase in sodium and water retention. High sodium may have a possible cofactoring influence, as it has been cross-sectionally associated with higher ouabain concentrations. High ouabain, in turn, was found in an animal model to prevent angiotensin 1 to 7 from exerting an anti–cell-swelling activity, which further promotes the activation of the stretch-activated chloride channel/ClC-3 channels. Activation of ClC-3 in response to tumor necrosis factor, leading to decrease of intracellular chloride, was found in an animal model to promote endothelial inflammation, via activation of nuclear factor-xB–related pathways. The possible consequences include proarrhythmia (because of uneven spread across the heart of the shortening of action potential, which in turn facilitates re-entry), enhanced endothelial inflammation, increase of blood pressure, and promotion of atherosclerosis. All of these phenomena may have led to increased mortality in hypertensive patients.

Much research still needs to be performed to confirm or disprove the mechanisms and the role of chloride level in cardiovascular pathology. The message for now is that those of patients with hypertension with lower chloride levels are at increased risk, and that based on the discriminant function calculated by McCallum et al, we should raise the lower cut-off for normal concentration of chloride from 95 to 100 mmol/L. The reported increase in risk seems not to be directly related to increase of blood pressure, as no such longitudinal relation between low chloride and blood pressure level was found by McCallum et al. However, a plethora of pathophysiologic features inherent to cardiovascular disease at large, and hypertension in particular, seem to be crucially influenced by chloride-dependent mechanisms. So, indeed, there is more about salt than just sodium.

Disclosures

None.

References

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Hypertension. 2013;62:829-830; originally published online August 26, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.01918
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/62/5/829

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