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Highlights in clinical autonomic neuroscience: how much salt is salubrious?

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ABSTRACT

Individuals differ in their preference for, sensitivity to, and physiologic need for, salt. Increasing the dietary intake of salt is considered first line treatment for orthostatic hypotension, orthostatic intolerance, and syncope. Dietary salt intake is also an important contributing cause for hypertension, which is the leading modifiable risk factor for mortality worldwide. Recent research calls into question the assumption that there is one ideal dose of dietary salt appropriate for everyone. Individualized salt recommendations for some patients should take into account orthostatic blood pressure patterns and in the future may also be guided by genetic information. An as yet unanswered question is whether high salt diets helpful in the treatment of orthostatic disorders would, if continued long-term, increase the risk of developing hypertension.

Introduction

Sodium is an essential nutrient that is necessary for cellular function and maintenance of blood pressure. Its principle dietary source is NaCl (salt), which not only enhances the taste of food but also acts as a preservative.

Increased salt intake is widely considered the first line of therapy for patients with orthostatic hypotension, orthostatic intolerance, and syncope, who experience symptoms of cerebral hypoperfusion in response to postural stress (Wieling et al., 2002). Current recommendations for the treatment of neurogenic orthostatic hypotension and orthostatic intolerance include daily salt intake of 10–20 g (180–360 mmol) (Low and Fealey, 2008; Low et al., 2008). Likewise, current recommendations for management of posturally related syncope include daily salt intake of at least 10 g (180 mmol) (El-Sayed and Hainsworth, 1996; Wieling et al., 2002, 2004). The rationale in each case is that the amount of sodium consumed determines extracellular fluid volume, and expanding intravascular plasma volume has been shown to improve orthostatic tolerance (El-Sayed and Hainsworth, 1996; Wieling et al., 2002, 2004).

If taken in excess, however, sodium may lead to hypertension and associated morbidity and mortality. Patients with orthostatic disorders may be surprised to receive recommendations to increase their salt intake when they have heard from other reliable sources that people in general should limit their salt intake.

Several recent articles report on new findings linking the complex interrelationships of salt, blood pressure, and the autonomic nervous system.

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Aburto, N.J., Ziolkovska, A., Hooper, L., et al. (Geneva, Switzerland). 2013. Effect of lower sodium intake on health: systematic review and meta-analyses. British Medical Journal 346, 1–20.

Article summary

This systematic review of 64 studies and meta-analysis of 56 studies was conducted under the direction of the World Health Organization for the purpose of updating their guidelines for sodium intake in adults and to establish guidelines for children. In adults, daily sodium intake of <2 g was associated with systolic and diastolic blood pressure reductions of 3.47 and 1.81 mm Hg, respectively, as compared to >2 g. Increased sodium intake correlated with increased risks for stroke (risk ratio = 1.24), stroke mortality (risk ratio = 1.63), and coronary heart disease mortality (risk ratio = 1.32). In children, reduced sodium intakes significantly reduced systolic and diastolic blood pressure by 0.84 and 0.87 mm Hg, respectively, in people with or without hypertension. Although some studies have shown increased epinephrine and norepinephrine levels acutely after reducing sodium intake, studies of more than four weeks' duration showed no enduring change in catecholamine levels with low sodium diets.

They concluded that adults as well as children would benefit from reducing sodium intake, stating that “almost all reductions in blood pressure are beneficial for health.”

Commentary

This review confirms the findings of previous meta-analyses and also finds that the evidence for health benefits of a low sodium diet extend to normotensive children. The recommendations for limiting sodium intake appear valid when applied to populations in general, which is

not to conclude that a low sodium diet would be healthy at all times for all individuals.

Habitual daily sodium intake is as much as 10 g (150 mmol, about 2 teaspoons of salt) in most industrialized societies and 12 g in parts of Eastern Europe and Asia (Strazzullo et al., 2009). The World Health Organization recommends a daily salt intake of less than 5 g for the prevention of cardiovascular disease and stroke (WHO, 2011). This is because higher levels of salt intake are strongly associated with raised blood pressure, which WHO estimates is the leading modifiable risk factor for mortality, accounting for 7.5 million deaths worldwide each year, or 12.8% of all deaths annually (WHO, 2011). Hypertension affects more than a quarter of the world's adult population (Kearney et al., 2005).

There is consensus, based on compelling evidence, that excess dietary sodium is the most important modifiable risk factor for essential hypertension (Strazzullo et al., 2009; Blaustein et al., 2011). High salt intake independent of hypertension is itself a risk factor for cardiovascular morbidity and mortality (Frisoli et al., 2012). The evidence indicates that a reduction of salt intake of 5 g a day could decrease the incidence of stroke by 23% and cardiovascular disease by 17% (Strazzullo et al., 2009).

The mechanisms by which dietary salt leads to elevated blood pressure are complex and incompletely understood. In addition to its immediate effects, salt also induces long-term effects on blood pressure that may be partly irreversible (Van Vliet and Montani, 2008; Frisoli et al., 2012). Research has focused on renal retention of salt, resetting of the arterial baroreflex, increased sympathetic nerve activity, arterial myocyte calcium signaling leading to increased myogenic tone in resistance arterioles, attenuated endothelial vasodilator responses, arterial oxidative stress, arterial lumen structural remodeling, and cerebrospinal fluid sodium levels (Blaustein et al., 2011; Franco and Oparil, 2006).

He, F.J., Li, J., MacGregor, G.A. (London, UK). 2013. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 4, CD004937.

Article summary

This update of the authors' 2004 meta-analysis (He and MacGregor, 2004) examined the long-term effects of modest reduction in salt intake on blood pressure in 34 randomized trials that had enrolled 3230 participants. They found that salt reduction achieved significant and dose-related falls in blood pressure in both hypertensive and normotensive individuals regardless of sex or ethnicity. Based on these findings, the authors recommended 3 g/d as the ideal long-term target for population salt intake, which is more stringent than the current recommendation of 5–6 g/d.

Commentary

The Institute of Medicine recommends an average sodium intake of less than 2.3 g/d (IOM, 2013), which is 5.85 g of NaCl. They concluded that studies on health outcomes have been insufficient to conclude that sodium intake of less than 2.3 g/d either increases or decreases the risk of heart disease, stroke, or mortality (IOM, 2013).

There are further clinical variables to consider in determining the ideal amount of salt for the individual patient. What most all of these studies did not consider were people with disorders of orthostatic tolerance. Recommendations that are valid for the population as a whole may not apply to them individually.

A further question, which has yet to be explored, is whether liberalization of salt intake in patients with orthostatic intolerance might over time increase their risk of eventually developing hypertension or related cardiovascular morbidity. Added salt is clearly beneficial in the short term (El-Sayed and Hainsworth, 1996; Wieling et al., 2002, 2004), but are there also potential long term adverse consequences? Prospective studies of syncope and orthostatic intolerance are needed that examine the relationship of salt to blood pressure changes over the long term. Whether added dietary salt for the patient with orthostatic intolerance is, in the balance, beneficial or potentially detrimental to blood pressure may depend on whether it restores or exceeds a healthy intravascular volume.

Carey, R.M., Schoeffel, C.D., Gildea, J.J. et al. (Charlottesville, Virginia, USA). 2012. Salt sensitivity of blood pressure is associated with polymorphisms in the sodium-bicarbonate cotransporter. Hypertension 60, 1359–1366.

Article summary

These investigators tested the hypothesis that salt sensitivity is associated with single nucleotide polymorphisms (SNPs) of the sodium-bicarbonate cotransporter gene (SLC4A5), which is associated with essential hypertension. The sodium-bicarbonate cotransporter participates in maintaining the homeostasis of intracellular pH in many organs, including the kidney, heart and brain.

The study recruited 55 hypertensive and 130 normotensive subjects, who were given a low sodium (10 mmol/d) or high sodium (300 mmol/d) diet for 7 days in random order. Salt sensitivity was defined as a > 7 mm Hg difference in mean arterial pressure between the two diets. Association analysis of known SNPs found that 3 variants were associated with salt sensitivity: 2 in SLC4A5 and 1 in the G protein-coupled receptor kinase-4 (GRK4). The authors hypothesized that, even if SLC4A5 were to play a minor role in sodium balance, a slight decrease of sodium excretion of only 0.1% over time could exert a substantial cumulative effect on blood pressure.

Commentary

Salt sensitivity, meaning a quantitative trait in which an increase in sodium intake leads to an increase in blood pressure, has been estimated to be present in approximately half of hypertensive and a quarter of normotensive individuals (Weinberger et al., 1986; Ando and Fujita, 2012). Salt sensitivity is higher in African-Americans, being present in 73% of hypertensives and 36% of normotensives (Svetkey et al., 1996). Since these studies have defined salt sensitivity in terms of the blood pressure response to short-term sodium ingestion or intravenous loading, if the long-term effects of excessive salt intake (Van Vliet and Montani, 2008) were taken into account, it is possible that the prevalence might be even higher. This study contributes an important piece to the puzzle of the molecular basis of heritable salt sensitivity.

Mallamaci, F., Leonardis, D., Pizzini, P., et al. (Reggio di Calabria, Italy) 2013. Procalcitonin and the inflammatory response to salt in essential hypertension: a randomized cross-over clinical trial. J Hypertension 31, 1424–1430.

Article summary

In order to assess the inflammatory phenotype associated with a very low salt diet, these investigators randomized 32 patients with essential hypertension to receive a 10–20 mmol per day sodium diet and either salt tablets to achieve a daily sodium intake of 200 mmol or placebo tablets for two weeks. The very low salt diet induced a pro-inflammatory phenotype characterized by increased levels of procalcitonin (PCT, increased by 33%) and tumor necrosis factor-α (TNF-α, increased by 9%) and a decreased level of adiponectin, an anti-inflammatory cytokine (decreased by 17%). No changes were observed in C-reactive protein or interleukin-6. These changes in inflammatory biomarkers, though significantly different from baseline,