With a Pinch of Salt
Does Reduced Dietary Sodium Consumption Promote Atherosclerosis?
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The strong positive correlation of dietary sodium intake with systolic blood pressure and the clear prognostic value of hypertension for cardiovascular disease have instigated nutritional guidelines recommending a reduction of average daily sodium intake to 1500 to 2300 mg/d (corresponding to 4–6 g of NaCl per day; current values for most Western countries lie between 9 and 12 g of NaCl per day).1 That such dietary restrictions effectively lower blood pressure has been clearly shown, and although it has proven much more difficult to show long-term effects of reduced dietary sodium on cardiovascular outcomes, studies in this direction seem to speak in favor of sodium restriction.2 Nevertheless, the rationale for restricting dietary sodium is subject to a highly emotional debate.3 Some “salt skeptics” argue that the increased activation state of the renin-angiotensin-aldosterone system (RAAS) triggered by reduction of dietary sodium could have untoward effects and that this underlies the disappointing outcomes of some studies looking at reduced sodium intake. At least in dyslipidemic mouse models, severe sodium restriction has been associated with increased atherosclerosis development, but a definite proof of an involvement of the RAAS herein was lacking. This prompted Tikellis et al4 to study atherosclerosis development in apolipoprotein E (ApoE)–deficient mice on various salt regimes.

Such studies have been performed by more groups but without demonstrating a definite link between sodium restriction and RAAS activation. The strength of the current article lies in the simple inclusion of treatment groups that combine dietary sodium restriction with an angiotensin-converting enzyme (ACE) inhibitor on the one hand and genetic RAAS activation with increased dietary sodium on the other. Compared with mice receiving a normal salt diet (0.30% NaCl, w/w), plasma aldosterone levels more than doubled in mice receiving a low-sodium diet (0.03% NaCl) but fell below the detection limit in animals receiving a high-salt (3%) diet. The ApoE−/− mice receiving a low-sodium diet developed fatty streaks associated with the increased vascular expression of adhesion molecules, the release of proinflammatory cytokines, and increased monocyte adherence to the endothelium of aortas isolated from these mice. Treating the mice with an inhibitor of the ACE completely prevented all of these atherosclerotic processes.4 Seeing as the involvement of the RAAS in the development of atherosclerosis has been repeatedly and convincingly demonstrated since the seminal results from the Heart Outcomes Prevention Evaluation Study,5 these results may not come as a big surprise. Nevertheless, it was this intervention that was missing in previous animal studies and that allows an interpretation of the results beyond pure speculation.

To further study the interplay between the systemic modulation of the RAAS by sodium intake and local vascular inflammation, Tikellis et al4 repeated the experiment in mice deficient for both ApoE−/− and the monocarboxypeptidase ACE2. ACE2 cleaves 1 amino acid from angiotensin II to generate angiotensin 1-7 (see Figure) and, thus, critically determines the balance between the proinflammatory, proatherogenic angiotensin II and its functional antagonist angiotensin 1-7. Correspondingly, ACE2-deficient mice develop atherosclerotic lesions on an ApoE−/− background.6,7 Indeed, the ACE2−/−/ApoE−/− mice used in this study likewise showed accelerated fatty streak formation to an extent similar to the mice that received a low-sodium diet and, whereas sodium restriction did not further aggravate atherogenesis, a high-sodium diet could suppress lesion formation in these mice.4

The presented data support the idea that excessive sodium restriction may have an unfavorable effect on atherosclerosis development, whereas a high-sodium diet can curb RAAS activation to avoid atherogenesis, at least in mice. It is difficult to extrapolate these findings to the human situation. It should be noted, for instance, that the mice showed only a very weak relationship between salt and blood pressure, with a 100-fold difference in dietary sodium intake between the low- and the high-sodium groups corresponding with relatively small (∼7 mm Hg) differences in blood pressure. For comparison, studies in humans indicate that roughly similar changes in blood pressure can be achieved by ∼2-fold changes in sodium intake.2 This brings the discussion to the incompletely understood concept of salt sensitivity. Salt sensitivity is not a binary trait but rather a continuum,1 and the mice used in this study are certainly at the far end of this spectrum. Salt sensitivity, that is, the steepness of the correlation between dietary sodium and blood pressure, is determined by multiple factors, and its (genetic) determinants are still eagerly sought for,8 but one of the contributors is the RAAS itself: changes in dietary sodium have only little impact on blood pressure in those individuals that have a...
Angiotensinogen

Sodium restriction + Renin - High sodium intake

Angiotensin I

ACE

Angiotensin II

ACE2, ACE

Angiotensin-(1-7)

AT₁

Vasoconstriction Vascular inflammation Aldosterone release Sodium & fluid retention

Mas

Vasodilatation Vasoprotection Blood pressure ↓

Figure. Schematic overview of the central players of the renin-angiotensin system. Renin, released by the kidney, cleaves a 10 amino acid fragment, angiotensin (Ang) I, from angiotensinogen that is produced by the liver. Ang I is considered inactive but can be cleaved by angiotensin-converting enzyme (ACE) into angiotensin II. Alternatively, Ang I can be metabolized by neutral endopeptidase (NEP) or by the combined action of ACE2 and ACE (via Ang-1-9, not shown) to Ang-(1-7). ACE2 also converts Ang II to Ang-(1-7). Stimulation of the Ang II type 1 (AT₁) receptor by Ang II has various local and systemic effects aimed at augmenting blood pressure, including sodium and water retention by the kidney, but also has proinflammatory effects on the vessel wall and circulating cells, whereas Ang-(1-7) through its own receptor has antihypertensive, vasodilating, and vasoprotective properties, functionally antagonizing Ang II. Sodium restriction promotes the release of renin, the rate-limiting enzyme of the cascade, from the juxtaglomerular cells of the kidney and enhances the production of all Ang peptides, but the net effect is enhanced signaling through the Ang II/AT₁ axis. Genetic deletion of ACE2 strongly tilts the Ang II/Ang-(1-7) equilibrium in favor of the former. Gray boxes indicate the interventions used by Tikellis et al⁴ to modulate renin-angiotensin-aldosterone system (RAAS) activity.

highly responsive RAAS. In other words, salt sensitivity indicates RAAS insensitivity and vice versa. Not completely coincidentally, those groups that have a high risk of blood pressure–associated morbidity (eg, individuals with hypertension or diabetes mellitus or blacks) generally have a less responsive RAAS.⁵ This is reassuring; it suggests that those who would profit the most from sodium restriction in terms of blood pressure reduction also run the least risk of accelerated atherosclerosis through RAAS activation.

Public health guidelines are subject to continuously increasing understanding. In the search for an optimal daily sodium dose, Tikellis et al⁴ make a valuable contribution to the discussion. It would be premature to translate the results from this mouse study into clinical practice, but they do underline the need for more substantial data on the impact of dietary changes on cardiovascular outcomes in humans. More information on clinical outcomes, however difficult to acquire, would not in the least also increase the acceptance rate of guidelines among the professionals that should be their advocates.

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None.

References


