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The Salted Artery and Angiotensin II Signaling: A Deadly Duo in Arterial Disease

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The average dietary sodium (NaCl) consumption of many modern humans has increased to at least 5- fold beyond that required for physiological needs [1]. Both an elevated sodium burden and Angiotensin II (Ang II) have signaling that has been linked to age-associated arterial remodeling [2–4], which is the major risk factor for the initiation and progression of atherosclerosis and hypertension (Table) [1–7]. In this issue of the *Journal of Hypertension*, Johansson et al explore the interactions among dietary NaCl, blood pressure and angiotensin II (Ang II) signaling, a major effector of the renin-angiotensin system (RAS) [8].

In addition to its well-known effects on arterial blood pressure, high NaCl intake, like other classic risk factors, affects arterial structure and function by altering the characteristics of vascular smooth muscle cells (VSMC), endothelial cells and the matrix in which these cells reside. Experimental evidence indicates that high NaCl induces arterial wall thickening, collagen and fibronectin deposition and collagen cross-linking in the absence of changes in arterial pressure in vivo [9, 10]; and induces hypertrophy of VSMC in vitro [11, 12]. Furthermore, excessive NaCl intake reduces the bioavailability of nitric oxide, via the superoxide anion generated from nitric oxide synthase, by increasing asymmetric dimethylarginine, an endogenous nitric oxide synthase inhibitor [13]. This reduces the production of nitric oxide by elevating ROS levels, i.e., peroxynitrite, due to an increase in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [14–17]. These NaCl-induced changes within the arterial wall are, in fact, the very ones that underlie arterial aging in numerous mammalian species and age-associated arterial diseases, i.e., hypertension, and atherosclerosis. These molecular events mimic, to an extraordinary extent, those that result from Ang II signaling (Table) [18–25]. A one month infusion of Ang II to young rats, in fact, also mimics the effects of NaCl and aging on the arterial wall [21]. Thus, Ang II signaling is a candidate mediator of the aforementioned effects of high NaCl on VSMC and endothelial cells and is linked to arterial inflammation.

Ang II signaling (Table) : (1) increases intercellular adhesion molecule-1 (ICAM-1) and reactive oxygen species (ROS), contributing to dysfunction of the local endothelial barrier and consequent inflammatory cell adhesion and transmigration [18, 19]; (2) activates calpain-1, a ubiquitous, cytosolic Ca^{2+} activated neutral protease, and the gradients of platelet-derived growth factor-BB (PDGF-BB) and monocyte chemoattractant protein-1 (MCP-1), facilitating infiltration of VSMC into the intima [21, 22, 24]; (3) activates matrix metalloproteinase type-2/9 (MMP-2/9) causing disruption of the basement membrane, internal elastin laminae and the arterial wall matrix, and endows VSMC with an enhanced migratory capacity [21–24]; and (4) activates a latent, powerful profibrogenic cytokine,

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transforming growth factor-beta1 (TGF- β 1) activation, resulting in production of collagen and fibronectin [25]. Chronic angiotensin-converting enzyme (ACE) inhibition markedly reduces these arterial structural effects in rodents [26, 27], and in hypertensive patients there is some evidence that ACE inhibitors decrease arterial inflammation, independent of changes in blood pressure [28].

It is known that arterial wall Ang II is over 1000-fold more abundant than circulating Ang II, is independently regulated, and plays an important role in vascular pathophysiology [18, 20, 28]. Early perspectives on the links between dietary high NaCl and the RAS, however, were dominated by the idea that a high salt intake reduces RAS activity, and the ensuing NaCl-dependent hypertension is referred to as “low renin hypertension” [7]. This perspective, however, was solely based on circulating renin activity, which indeed decreases following NaCl loading, but ignored the local Ang II contribution. But, emerging evidence indicates that NaCl upregulates the arterial wall Ang II precursor, angiotensinogen, enhances Ang I conversion into Ang II by ACE activity, and increases Ang II signaling molecules, NADPH oxidase activity and fibronectin expression within the arterial wall [16, 17, 29, 30]. High salt intake increases aortic AT1 receptor mRNA, AT1 receptor density, and Ang II binding capacity in vivo [29, 31, 32]. Furthermore, incubation of VSMC in an increased NaCl concentration caused a time-dependent elevation of AT1 receptor mRNA levels; and the NaCl-induced AT1 receptor upregulation led to an enhanced functional response of VSMCs upon stimulation with Ang II, via an increase of intracellular calcium in response to the high salt concentration [32]. Thus, NaCl could directly induce AT1 receptor upregulation in vitro as well as in vivo.

Since NaCl-associated arterial inflammation and structural changes appear to be mediated by AT1 signaling, it is reasonable to assume a synergism of NaCl and Ang II with respect to their impact on the arterial wall. Indeed, Wistar Kyoto rats (WKY) fed with a long-term high NaCl^{diet} does not demonstrate aortic structural changes. But, in spontaneous hypertensive rats (SHR), in which arterial AT1 receptors and ACE activity are upregulated, substantial aortic structural changes including intimal-medial thickening, and collagen deposition developed without any further blood pressure alteration compared to control animals [33–35]. In addition, stroke-prone SHR rats (SHRsp) on a high-sodium diet are characterized by increased expression of the fetal non-muscle myosin chain subunit (NHMC) in aortic VSMC, a phenotype shift also is observed in aged human aorta enriched with abundant levels of Ang II, AT1, and ACE [20, 36]. Ang II may reprogram differentiated VSMC into dedifferentiated cells via increased expression of NHMC [37]. In this issue of the *Journal of Hypertension*, Johansson ME et al have studied the combination of dietary high NaCl and Ang II infusion of ApoE^{-/-} mice [8]. Impressively, while a high salt diet combined with Ang II did not amplify blood pressure, it did further increase the extent of plaque, including collagen and macrophages, in both the innominate and thoracic arteries compared to control animals [8]. These effects were associated with amplified levels of isoprostane, biomarker widely employed clinically to detect increased ROS [38].

In summary, proteins within the arterial wall are similarly reprogrammed, by dietary high salt, aging, hypertension, and atherosclerosis (Table). This arterial proinflammatory profile is strikingly similar to that effected by increased arterial Ang II signaling via AT1. Ang II-synergistic interactions with NaCl and aging, and with other well-known human risk factors, e.g., altered lipid metabolism, smoking, and lack of exercise, render the arterial wall fertile soil for facilitation of the initiation and progression of the quintessential arterial diseases of our society, hypertension, and atherosclerosis.

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References

1. Karppanen H, Mervaala E. Sodium intake and hypertension. *Prog Cardiovasc Dis.* 2006; 49:59–75. [PubMed: 17046432]
2. Aviv A. Salt consumption, reactive oxygen species and cardiovascular ageing: a hypothetical link. *J Hypertens.* 2002; 20:555–559. [PubMed: 11910279]
3. Safar ME, Thuilliez C, Richard V, Benetos A. Pressure-independent contribution of sodium to large artery structure and function in hypertension. *Cardiovasc Res.* 2000; 46:269–276. [PubMed: 10773231]
4. Avolio A. Genetic and environmental factors in the function and structure of the arterial wall. *Hypertension.* 1995; 26:34–37. [PubMed: 7607729]
5. Lakatta EG. Central arterial aging and the epidemic of systolic hypertension and atherosclerosis. *J Am Soc Hypertens.* 2007; 1:302–340. [PubMed: 20409863]
6. Wang, M.; Lakatta, EG. Chapter 9. Central Arterial Aging: Humans to Molecules Hypertension in the elderly. In: Safar, Michel E.; O'Rourke, Michel E., editors. *Handbook of Hypertension.* Vol. 23. Elsevier; 2006. p. 137-160.
7. Bagrov AY, Lakatta EG. The dietary sodium-blood pressure plot “stiffens”. *Hypertension.* 2004; 44:22–24. [PubMed: 15173129]
8. Johansson ME, Berberg E, Andersson AJ, Bie P, Skott O, Gan LM, et al. High salted diet combined with elevated angiotensin II accelerates atherosclerosis in ApoE^{-/-} mice. *J Hypertens.* 2008 in print.
9. Tobian L, Hanlon S. High sodium chloride diets injure arteries and raise mortality without changing blood pressure. *Hypertension.* 1990; 15:900–903. [PubMed: 2351440]
10. Tamura K, Chiba E, Yokoyama N, Sumida Y, Yabana M, Tamura N, et al. Renin-angiotensin system and fibronectin gene expression in Dahl Iwai salt-sensitive and salt-resistant rats. *J Hypertension.* 1999; 17:81–89.
11. Gu JW, Anand V, Shek EW, Moore MC, Brady AL, Kelly WC, et al. Sodium induces hypertrophy of cultured myocardial myoblasts and vascular smooth muscle cells. *Hypertension.* 1998; 31:1083–1087. [PubMed: 9576118]
12. Yamori Y, Igawa T, Tagami M, Kanbe T, Nara Y, Kihara M, et al. Trophic influence on cardiovascular structural changes in hypertension. *Hypertension.* 1984; 6(Suppl III):27–32. [PubMed: 6693146]
13. Scuteri A, Stuehlinger MC, Cooke JP, Wright JG, Lakatta EG, Anderson DE, et al. Nitric oxide inhibition as a mechanism for blood pressure increase during salt loading in normotensive postmenopausal women. *J Hypertens.* 2003; 21:1339–1346. [PubMed: 12817182]
14. Nurkiewicz TR, Boegehold MA. High salt intake reduces endothelium-dependent dilation of mouse arterioles via superoxide anion generated from nitric oxide synthase. *Am J Physiol Regul Integr Comp Physiol.* 2007; 292:R1550–R1556. [PubMed: 17138723]
15. Meng S, Cason GW, Gannon AW, Racusen LC, Manning RD Jr. Oxidative stress in Dahl salt-sensitive hypertension. *Hypertension.* 2003; 41:1346–1352. [PubMed: 12719439]
16. Bayorh MA, Ganafa AA, Eatman D, Walton M, Feuerstein GZ. Simvastatin and losartan enhance nitric oxide and reduce oxidative stress in salt-induced hypertension. *Am J Hypertens.* 2005; 18:1496–1502. [PubMed: 16280288]
17. Zhou MS, Hernandez Schulman I, Pagano PJ, Jaimes EA, et al. Reduced NAD(P)H oxidase in low renin hypertension: link among angiotensin II, atherogenesis, and blood pressure. *Hypertension.* 2006; 47:81–86. [PubMed: 16344366]

18. Daugherty A, Cassis L. Angiotensin II-mediated development of vascular diseases. *Trends Cardiovasc Med*. 2004; 14:117–120. [PubMed: 15121160]
19. Csiszar A, Wang M, Lakatta EG, Ungvari ZI. Inflammation and endothelial dysfunction during aging: role of NF- κ B. *J Appl Physiol*. 2008; 105:1333–1341. [PubMed: 18599677]
20. Wang M, Zhang J, Jiang LQ, Spinetti G, Pintus G, Monticone R, et al. Proinflammatory profile within the grossly normal aged human aortic wall. *Hypertension*. 2007; 50:219–227. [PubMed: 17452499]
21. Wang M, Zhang J, Spinetti G, Jiang L, Monticone R, Zhao D, et al. Angiotensin II activates matrix metalloproteinase type II and mimics age-associated carotid arterial remodeling in young rats. *Am J Pathol*. 2005; 167:1429–1442.
22. Jiang L, Wang M, Zhang J, Monticone RE, Telljohann R, Spinetti G, et al. Increased aortic calpain-1 activity mediates age-associated angiotensin II signaling of vascular smooth muscle cells. *PLoS ONE*. 2008; 3:e2231. [PubMed: 18493299]
23. Wang M, Takagi G, Asai K, Resuello RG, Natividad FF, Vatner DE, et al. Aging increases aortic MMP-2 activity and angiotensin II in nonhuman primates. *Hypertension*. 2003; 41:1308–1316. [PubMed: 12743015]
24. Spinetti G, Wang M, Monticone R, Zhang J, Zhao D, Lakatta EG. Rat aortic MCP-1 and its receptor CCR2 increase with age and alter vascular smooth muscle cell function. *Arterioscler Thromb Vasc Biol*. 2004; 24:1397–1402. [PubMed: 15178559]
25. Wang M, Zhao D, Spinetti G, Zhang J, Jiang LQ, Pintus G, et al. Matrix metalloproteinase 2 activation of transforming growth factor-beta1 (TGF-beta1) and TGF-beta1-type II receptor signaling within the aged arterial wall. *Arterioscler Thromb Vasc Biol*. 2006; 26:1503–1509. [PubMed: 16690877]
26. Michel JB, Heudes D, Michel O, Poitevin P, Phillippe M, Scalbert E, et al. Effect of chronic ANGI-converting enzyme inhibition on aging processes: II: Large arteries. *Am J Physiol*. 1994; 267:R124–R135. [PubMed: 8048614]
27. Huang W, Alhenc Gelas F, Osborne-Pellegrin MJ. Protection of the arterial internal elastic lamina by inhibition of the renin-angiotensin system in the rat. *Circ Res*. 1998; 82:879–890. [PubMed: 9576107]
28. Ferrario CM, Strawn WB. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *Am J Cardiol*. 2006; 98:121–128. [PubMed: 16784934]
29. Tamura K, Chiba E, Yokoyama N, Sumida Y, Yabana M, Tamura N, et al. Renin-angiotensin system and fibronectin gene expression in Dahl Iwai salt-sensitive and salt-resistant rats. *J Hypertension*. 1999; 17:81–89.
30. Boddi M, Poggesi L, Coppo M, Zarone N, Sacchi S, Tania C, et al. Human vascular renin-angiotensin system and its functional changes in relation to different sodium intakes. *Hypertension*. 1998; 31:836–838. [PubMed: 9495269]
31. Wang DH, Du Y. Regulation of vascular type 1 angiotensin II receptor in hypertension and sodium loading: role of angiotensin II. *J Hypertens*. 1998; 16:467–475. [PubMed: 9797192]
32. Nickenig G, Strehlow K, Roeling J, Zolk O, Knorr A, Böhm M. Salt Induces Vascular AT₁ Receptor Overexpression In Vitro and In Vivo. *Hypertension*. 1998; 31:1272–1277. [PubMed: 9622141]
33. Partovian C, Benetos A, Pommiès JP, Mischler W, Safar ME. Effects of a chronic high-salt diet on large artery structure: role of endogenous bradykinin. *Am J Physiol*. 1998; 274:H1423–1428. [PubMed: 9612345]
34. Limas C, Westrum B, Limas CJ, Cohn JN. Effect of salt on the vascular lesions of spontaneously hypertensive rats. *Hypertension*. 1980; 2:477–489. [PubMed: 7399629]
35. Linz W, Jessen T, Becker RH, Schölkens BA, Wiemer G. Long-term ACE inhibition doubles lifespan of hypertensive rats. *Circulation*. 1997; 96:3164–3172. [PubMed: 9386189]
36. Contard F, Sabri A, Glukhova M, Sartore S, Marotte F, Pomies JP, et al. Arterial smooth muscle cell phenotype in stroke-prone spontaneously hypertensive rats. *Hypertension*. 1993; 22:665–676. [PubMed: 8225526]

37. Yamada T, Kondo T, Numaguchi Y, Tsuzuki M, Matsubara T, Manabe I, et al. Angiotensin II receptor blocker inhibits neointimal hyperplasia through regulation of smooth muscle-like progenitor cells. *Arterioscler Thromb Vasc Biol.* 2007; 27:2363–2369. [PubMed: 17717297]
38. Rahman I, Biswas SK. Non-invasive biomarkers of oxidative stress: reproducibility and methodological issues. *Redox Rep.* 2004; 9:125–143. [PubMed: 15327743]

Table
Arterial Remodeling: Impact of Dietary Sodium, Aging, Hypertension, and Atherosclerosis and Ang II Signaling

	Dietary Salt	Aging					Hypertension	Atherosclerosis	Ang II Signaling
		Humans (>65 yrs)	Monkeys (15–20 yrs)	Rats (24–30 mos)	Rabbits (3–6 yrs)				
Luminal dilation	?	+	+	+	+		?	?	?
↑ Stiffness	+	+	+	+	+		+	+	+
Endothelial dysfunction	+	+	+	+	+		+	+	+
Diffuse Intimal Thickening	+	+	+	+	+		+	+	+
Lipid involvement	±	–	–	–	–		±	+	+
↑ VSMC number	+	+	+	+	+		+	+	+
Macrophages	±	+	–	–	+		+	+	+
↑ Matrix	+	+	+	+	+		+	+	+
↑ Local ACE-ANGII- AT1	+	+	+	+	+		+	+	+
MMP/Calpain dysregulation	+	+	+	+	?		+	+	+
↑ MCP-1/CCR2	+	+	+	+	+		+	+	+
↑ ICAM-1	+	?	?	+	?		+	+	+
↑ TGF-D	+	+	+	+	?		+	+	+
↑ NADPH Oxidase	+	?	?	+	?		+	+	+
↓ Nitric Oxide Bioavailabilit	+	?	?	+	+		+	+	+
HYPERTENSION	±	±	±	±	?		+	±	+
ATHEROSCLEROSIS	±	±	–	–	–		±	+	+

?, information unknown