High Sodium Intake Decreases Pressure-Induced (Myogenic) Tone and Flow-Induced Dilation in Resistance Arteries From Hypertensive Rats

Khalid Matrougui, Pierre Schiavi, David Guez, Daniel Henrion

Abstract—High sodium intake has been associated with a higher blood pressure level. Resistance arteries are the main determinants of blood pressure. They are largely regulated by pressure (tensile stress)—induced tone (myogenic tone, MT) and by flow (shear stress)—induced dilation (FD). Thus, we studied the effect of NaCl (8%) intake for 8 weeks on FD and MT in mesenteric resistance arteries of spontaneously hypertensive rats. Arteries were cannulated and mounted in an arteriograph. Intraluminal diameter was measured continuously. High NaCl intake increased mean arterial pressure (186±5 to 217±6 mm Hg, P<0.01). Passive arterial diameter ranged from 112±6 to 185±9 μm (pressure from 25 to 125 mm Hg, no effect of NaCl). MT developed in response to pressure (tone from 89±1% to 83±3% of passive diameter, 25 to 125 mm Hg). High NaCl intake significantly decreased MT (89±1% versus 83±3% of passive diameter when pressure was 125 mm Hg, P<0.023). High NaCl intake also decreased FD (6.5±0.8 versus 10±1.3 μm dilation under a pressure of 100 mm Hg and a flow rate of 160 μL/min, P<0.012). Thus, high salt intake decreased both flow (shear stress)—induced dilation and pressure (tensile stress)—induced tone in mesenteric resistance arteries. These findings might reflect attenuation by NaCl of flow and pressure mechanosensor processes. (Hypertension. 1998; 32:176-179.)

Key Words: myogenic tone ■ shear stress ■ blood vessels ■ resistance arteries ■ sodium

Flow (shear stress)—induced dilation and pressure (tensile stress)—induced tone (myogenic tone) are two fundamental mechanisms for the control of vascular tone. Shear stress is a potent stimulus for vascular endothelial cells, triggering the release of vasoactive agents such as nitric oxide (NO), cyclooxygenase products, hyperpolarizing factors, and contracting factors.1–3 Myogenic tone develops on stretch4,5 and is generally independent of the endothelium.6 It is opposed by flow-induced dilation in vitro as well as in vivo.1–3 High salt intake has been widely involved in the genesis of hypertension.10–13 Previous studies have shown a specific sensitivity of flow-induced dilation and myogenic tone to small changes in extracellular sodium concentration.1,14 We hypothesized that flow-induced dilation and myogenic tone might be selectively influenced by high salt intake. We used mesenteric resistance arteries from spontaneously hypertensive rats (SHR) submitted to high dietary salt intake. Vessels were isolated in vitro in an arteriograph, and pressure (myogenic)—induced tone and flow (shear stress)—induced dilation were determined. Myogenic tone was determined compared with passive arterial diameter, which depends on the structure of the arterial wall.3,4,15,16

Methods

Two groups of 6-week-old SHR (n=19) were housed separately. One group was fed a normal NaCl diet (0.4%, control group, n=9) while the other group was fed a high NaCl diet (8%, high sodium group, n=10). After 8 weeks, rats were anesthetized with pentobarbital (50 mg/kg IP), and the carotid artery was cannulated (ID, 0.6 mm) to measure blood pressure (pressure transducer, Gould P10EZ). A segment of mesenteric resistance artery (140 μm ID, 2 mm long) was isolated and cannulated at both ends in an arteriograph (Living System Instrumentation Inc) as described previously.15,16 The segment was bathed in physiological salt solution (in mmol/L): 135.0 NaCl, 15.0 NaHCO3, 4.6 KCl, 1.5 CaCl2, 1.2 MgSO4, 11.0 glucose, and 10.0 HEPES (pH was 7.4, PO2 was 160 mm Hg, and PCO2 was 37 mm Hg). The pressure in both ends of the artery segment was monitored using pressure transducers.15,16 Flow in the vessel could be generated through the distal pipette with a peristaltic pump. Pressure in the proximal end of the vessel was controlled by a servo-controlled peristaltic pump (no recirculation of the perfusing solution). When flow was applied and pressure increased, the difference in pressure between distal and proximal ends of the vessel was changed so that pressure could be increased without change in flow. This assumes that the 2 pipettes provide the same resistance to flow; therefore, pairs of pipettes were selected to satisfy the prerequisite. In these conditions, the average pressure between distal and proximal pressures can be assumed to be representative of lumen pressure.15,16 Thus, pressure and flow rate could be changed independently.15,16 Arterial diameter was measured and recorded continuously17 using a video monitoring system (Living System Instrumentation Inc).

Equilibrium diameter changes were measured for intraluminal pressure set at 25, 50, 75, 100, and 125 mm Hg (no flow). Pressure was then set at 100 mm Hg, and flow was increased by steps from 3 to 160 μL/min. Arterial diameter was measured at each step at the
The integrity of the endothelium was assessed by testing the vasodilator effect of acetylcholine (1 μmol/L) after preconstriction with phenylephrine (0.01 μmol/L) to the perfusion and superfusion solutions. At the end of each experiment, arteries were perfused and superfused with a Ca²⁺-free physiological salt solution containing EGTA (2 mmol/L) and sodium nitroprusside (100 μmol/L) to determine the passive diameter of the arterial segments under the different levels of pressure used (25 to 125 mm Hg). Data was collected using a Biopac MP 100 data acquisition system. Results are given in micrometers (10⁻⁶ m). The diameter was measured by imaging and using image analysis software. For the statistical analysis, the differences between the groups were assessed using one-way ANOVA or two-factor ANOVA for repeated measurements. The significance level was set at *P < 0.05.

**Statistical Analysis**

Results are expressed as mean ± SE. Significance of the differences between the different groups was determined by 1- or 2-factor ANOVA, or ANOVA for consecutive measurements when appropriate. Values of *P* < 0.05 were considered to be significant.

**Drugs**

All reagents were purchased from Sigma Chemical Co.

**Results**

Mean arterial blood pressure significantly increased in rats fed a high NaCl diet (186 ± 5 versus 217 ± 6 mm Hg, *P* < 0.01). High NaCl decreased body weight (284 ± 10 to 265 ± 10 g, *P* < 0.01) and increased the ratio of heart weight to body weight (3.45 ± 0.9 to 4.36 ± 0.13 mg/g, *P* < 0.01).

Figure 1 shows typical recordings obtained in mesenteric resistance arteries isolated from SHR with normal or high NaCl intake and mounted in vitro in an arteriograph. Stepwise increases in flow induced a significant dilation in mesenteric resistance arteries (Figures 1 and 2). Flow-induced dilation was lower in rats with a high sodium intake (Figure 2). In both groups, L-NAME (10 μmol/L) and indomethacin (10 μmol/mL) did not significantly change flow-induced dilation. For example, with a pressure of 100 mm Hg and a flow rate of 65 μL/min, the diameter was 152 ± 7, 151 ± 7 after L-NAME, and 152 ± 8 μm after indomethacin (group with 0.4% NaCl). In the group with 8% NaCl, the diameter was 167 ± 7, 166 ± 8 after L-NAME, and 165 ± 6 μm after indomethacin. Passive arterial diameter ranged from 114 ± 4 to 186 ± 6 μm in rats fed a high NaCl and from 112 ± 6 to 185 ± 9 μm in control rats (no significant difference between groups). Stepwise increases in pressure (25 to 125 mm Hg, no flow) induced the development of myogenic tone that was significantly lowered by the high NaCl diet (Figure 3). The addition of L-NAME (10 μmol/L) and indomethacin (10 μmol/L) had no significant effect on myogenic tone in both groups (not shown).

The integrity of the endothelium was assessed by testing the vasodilator effect of acetylcholine (1 μmol/L) after a preconstriction with phenylephrine (0.01 μmol/L). Phenylephrine (0.01 μmol/L) induced a contraction in mesenteric resistance arteries from SHR (diameter from 100 ± 5 to 19 ± 6 μm) and in SHR fed a high NaCl diet (109 ± 15 to 12 ± 8 μm; no significant difference between groups). Acetylcholine (1 μmol/L) induced vasodilation of phenylephrine (0.01 μmol/L)–induced contraction in SHR (diameter from 19 ± 6 to 103 ± 4 μm) and in SHR fed a high NaCl diet (12 ± 8 to 113 ± 14 μm; no significant difference between groups).

**Figure 1.** Typical recordings show the changes in diameter in response to increasing flow rates, under a pressure of 100 mm Hg, in resistance mesenteric arterial segments isolated from spontaneously hypertensive rats with normal (A) or high (B) sodium intake.

**Figure 2.** Flow (3 to 160 μL/min)-induced dilation in resistance mesenteric arteries isolated from spontaneously hypertensive rats with a normal (n=9) or high (n=10) salt intake. Data is expressed as change in diameter in micrometers (mean ± SE). *P* < 0.001, high versus normal salt intake, 2-factor ANOVA for repeated measures.

**Figure 3.** Myogenic tone determined in resistance mesenteric artery segments isolated from spontaneously hypertensive rats with a normal (n=9) or high (n=10) salt intake. Myogenic tone was expressed as percentage of passive diameter (mean ± SE), *P* < 0.001, normal versus high salt intake, 2-factor ANOVA for repeated measures.
High Sodium Intake Alters Vascular Tone

Discussion

The major finding of the present study is that high NaCl intake decreased both flow-induced dilation and myogenic tone in SHR.

That high salt intake increased blood pressure and heart weight and decreased body weight in SHR is in agreement with previous studies. High salt intake causes an exaggerated development of hypertension in rats genetically predisposed to hypertension, such as SHR. It should be noted that this sensitivity to NaCl may not apply to other strains of rats or to nonsensitive subjects in other species.

Flow-induced dilation in SHR was resistant to NO synthase and cyclooxygenase inhibition, which is consistent with our previous studies. High salt intake decreased flow-induced dilation. A decreased response to flow after sodium load has been previously shown in Dahl rats. In addition, high sodium intake lowers endothelium-dependent vasodilation to acetylcholine and decreases NO synthase activity in rats. Nevertheless, in SHR neither NO nor cyclooxygenase derivatives are efficiently involved in flow-induced dilation in mesenteric arteries, as shown in the present and in previous studies. Thus, the decreased flow-induced dilation found in the present study after high sodium intake may not involve a change in NO synthase or cyclooxygenase activity. In addition to the possibilities given below, one explanation could be that contracting agents released on flow stimulation were increased by the high NaCl diet. Indeed, endothelin-1 is released by flow, and its production increases after high salt intake.

In resistance arteries, myogenic tone decreased after high salt intake. This may look paradoxical because salt loading increased blood pressure. Nevertheless, myogenic tone may not be primarily responsible for the increased blood pressure after a sodium load. Decreased myogenic tone could reflect an adaptation to increased vascular tone originating from other mechanisms responsible for the increased blood pressure. In Dahl salt-sensitive rats, high NaCl intake impairs myogenic tone in renal arterioles. Indeed, high salt increases sympathetic activity. As myogenic tone in resistance arterioles is strongly potentiated by sympathetic stimulation, a chronic overstimulation of myogenic tone by norepinephrine might downregulate myogenic tone. Another possibility is that such downregulation results from an increased intracellular calcium concentration after high salt intake. Such a rise in intracellular calcium concentration might result from a decrease in Na⁺/K⁺ ATPase activity. An initial defect in renal function would induce a rise in endogenous inhibitor(s) of the pump (ouabain-like factors), which would in turn decrease Na⁺/K⁺ exchanges and thus increase vascular tone. It has been shown that Na⁺/K⁺ ATPase blockade with ouabain increases sarcoplasmic reticulum calcium filling and thus increases vascular responsiveness to vasoconstrictor agents. Indeed, calcium sequestration by the sarcoplasmic reticulum increases in vascular cells from rats with a high salt intake. Sarcoplasmic reticulum calcium is also involved in endothelial cell response to flow. Another possibility to explain a decrease in both myogenic tone and flow-induced dilation is that high salt intake could affect mechanosensors to flow and pressure, both sensitive to small changes in extracellular sodium and probably located in the extracellular matrix. Even without a detectable change in the circulating level of sodium, the extracellular glycosaminoglycans might bind a larger amount of cations, mainly sodium, and then increase the extracellular concentrations in response to mechanical stimuli as they release the cations on shear stress stimulation.

In conclusion, chronic high salt intake in SHR decreased flow-induced dilation and myogenic tone, reflecting a possible structural and/or functional change in the signaling mechanisms in endothelial and smooth muscle cells.

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References


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