The Mechanism of the Acute Effect of Sodium Chloride on Blood Pressure (35309)

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While it is well established that acute changes in plasma sodium chloride concentration can affect blood pressure, the mechanism of this effect is not clear. Studies in perfused vascular beds indicate that the sodium chloride *per se* is not vasoactive; its effect on resistance seems to result indirectly from osmotic shift of water rather than from some direct action (1). In an attempt to determine whether this also applies to the intact cardiovascular system as a whole, blood pressure was measured in the anesthetized dog during acute selective sodium chloride depletion without water depletion; total osmotic pressure of extracellular fluid was held constant to prevent osmotic shift of water into cells.

Methods. This was accomplished by injecting a potent diuretic intravenously and then exactly replacing the water lost in the urine with an isosomotic modified Ringer's solution in which mannitol was substituted for the sodium chloride. The method has been described in detail elsewhere (2). In brief, dogs having an average weight of 18.5 kg were anesthetized with sodium pentobarbital and ventilated artificially. The femoral artery, femoral vein, and urinary bladder were catheterized for measurement of arterial pressure, infusion of the solution, and measurement of urine flow, respectively. Furosemide, 20 mg/kg, was then injected intravenously and immediately afterward 500 ml of the replacement solution were injected intravenously to stimulate urine flow. When 500 ml urine had been excreted, the replacement solution was infused intravenously exactly at the rate of urine flow. Particular attention was given the depth of anesthesia; supplemental doses of pentobarbital were given whenever a conjunctival reflex appeared. Arterial blood was sampled periodically. The urine was pooled and sampled at the end of the experiment. Plasma and urine osmolality were measured by the freezing point depression method, potassium and sodium by flame photometry, and magnesium and calcium by atomic absorption. Blood pH was measured by the method of Astrup and hematocrit by capillary centrifugation.

In eight control experiments the replacement solution contained (g/liter): NaCl, 7.2; $NaHCO_3$, 1.8; KCl, 0.3; $MgCl_2 \cdot 6H_2O$, 0.5; and Ca gluconate, 1.0. In eight experiments designed to selectively lower the plasma sodium concentration, mannitol was substituted for the NaCl and $NaHCO_3$ in the solution. In both groups, an isotonic solution of KCl was also infused intravenously via a forelimb vein at 1.23 ml/min during the entire post-furosemide period to obviate a fall in the plasma potassium concentration (2). The volume of this fluid as well as that of the blood samples were taken into account in arriving at a precise water balance.

Results. Table I shows that when mannitol was substituted for the sodium chloride and sodium bicarbonate in the replacement fluid, plasma sodium concentration fell 29 mEq/liter in 76 min. Plasma osmolality, $[K^+]$ $[Mg^{2+}]$, $[Ca^{2+}]$, blood pH and hematocrit did not change appreciably. The findings were similar in the control experiments, except that here the sodium concentration also remained constant. Mean arterial pressure rose 14 mm Hg in the experimental group and 12 mm Hg in the control group. The reason for the small blood pressure rise in both groups is unknown but could be, at least in part, related to lightening of the anesthesia and renin release. Heart rate did not change in either group.

TABLE I. Arterial Plasma Osmolality, Plasma Cation Concentration, Blood pH, Hematocrit, and Blood Pressure in the Control and Experimental Groups.[a]

t (min)	V (ml)	Osm (mOsm/kg)	(mEq/liter) Na	K	Ca	Mg	pH	Hct (%)	(mm Hg) P_M	P_S	P_D
Control ($n = 8$)											
0	0	309 ± 3	155 ± 2	3.2 ± 0.1	3.9 ± 0.1	1.84 ± 0.07	7.40 ± 0.02	34.5 ± 1.5	111 ± 7	143 ± 10	100 ± 6
65 ± 14	561 ± 10	312 ± 2	156 ± 2	3.4 ± 0.1	3.9 ± 0.1	1.88 ± 0.09	7.40 ± 0.02	39.9 ± 1.9	123 ± 5	155 ± 11	111 ± 4
Experimental ($n = 8$)											
0	0	300 ± 2	154 ± 2	4.0 ± 0.1	4.2 ± 0.1	1.99 ± 0.05	7.39 ± 0.02	38.8 ± 1.5	98 ± 7	127 ± 8	84 ± 7
48 ± 6	548 ± 10	303 ± 2	139 ± 2	3.7 ± 0.1	4.3 ± 0.1	1.89 ± 0.04	7.36 ± 0.04	42.6 ± 1.4	111 ± 6	141 ± 7	99 ± 6
76 ± 8	1034 ± 69	304 ± 1	125 ± 3	4.0 ± 0.1	4.2 ± 0.1	1.86 ± 0.05	7.35 ± 0.02	40.6 ± 1.5	112 ± 8	140 ± 9	96 ± 7

[a] Values represent means ± SE; t = time after injection of furosemide; V = volume of replacement solution (and urine); P_M = mean arterial pressure; P_S = systolic arterial pressure; P_D = diastolic arterial pressure.

The osmolality and concentrations of sodium, potassium, calcium, and magnesium in the pooled urine were 335 mOsm/kg, 124 mEq/liter, 31 mEq/liter, 2.7 mEq/liter, and 5.39 mEq/liter in the control group. The corresponding values in the experimental group were 308, 90, 24, 2.2, and 1.96, respectively. The latter animals excreted 1034 ml of urine and received no sodium. Hence they lost 93 mEq of sodium in 76 min. Assuming an extracellular volume of 3700 ml, calculated extracellular sodium in the control state equaled 570 mEq. Seventeen percent of this appeared in the urine. This agrees with the 19% fall in plasma sodium concentration observed.

Discussion. Studies in perfused vascular beds have failed to demonstrate that sodium chloride *per se* affects vascular resistance (1, 3). In the dog forelimb (1), for example, an isosmotic reduction of the sodium chloride concentration in the perfusing blood over ranges which occur naturally has no discernible effect on blood vessel geometry. Constriction becomes manifest only when a fall in osmolality accompanies the fall in sodium chloride concentration. Elevation of the sodium chloride concentration reduces forelimb vascular resistance. This effect, however, cannot be attributed to sodium chloride *per se* since it also occurs when osmolality is equally elevated with other agents, dextrose and urea for example. Thus these effects seem to result from osmotic shift of water rather than from a specific action of sodium chloride.

Data from isolated muscle (4–8) show that hyposmolality causes cell hydration, a reduction in the intracellular potassium concentration, a decrease in the membrane potential, and cellular contraction. The opposite is produced by hyperosmolality. Other data suggest that sodium competes with calcium for a carrier in the membrane such that reducing extracellular sodium concentration results in calcium influx and cell contraction (9). The latter mechanism however is not compatible with the absence of a response in perfused vascular beds when extracellular sodium concentration is reduced without changing osmolality or with the similarity of the responses seen when osmolality is raised with sodium chloride, dextrose, or urea (1, 3).

The findings in this study are in agreement with those obtained from perfused vascular beds. Blood pressure failed to change relative to the control series when plasma sodium concentration was selectively reduced over ranges which occur naturally without changing osmolality. Apparently the changes in blood pressure seen with acute manipulation of the total body sodium chloride concentration (10–14) also result via associated changes in extracellular osmolality. These changes in osmolality redistribute total body water such that blood volume and cell hydration are altered (10, 15, 16). These alterations in turn influence cardiac output, total peripheral resistance, and hence blood pressure. Thus acute pure salt depletion lowers osmolality resulting in osmotic shift of extracellular water into cells (10). This lowers blood volume and hydrates vascular and red cells. The fall in blood volume decreases cardiac output via the Starling mechanism and increases resistance via the baroreceptor system (10, 11). Cell hydration also increases resistance (1, 3) through (i) activation of the contractile machinery of the vascular smooth muscle (see above and 4–8), (ii) luminal bulging of endothelial cells, and (iii) swelling of red cells. Hemoconcentration (10, 11) may also play a role in the increased resistance. The fall in cardiac output is proportionately greater than the rise in peripheral resistance and the blood pressure falls (10, 11).

Acute hypernatremia on the other hand raises osmolality resulting in osmotic shift of cellular water into the extracellular compartment (16). This raises blood volume (15) and dehydrates cells (16). The hypervolemia increases cardiac output via the Starling mechanism (13–15) and momentarily decreases resistance via the baroreceptor mechanism; cell dehydration also decreases resistance (1, 3, 6, 12–15) via deactivation of the contractile machinery of the vascular smooth muscle (see above and 4–8) and shrinkage of endothelial and red cells (14). Hemodilution (13–15) may also play a role in the decreased resistance. The fall in resistance is proportionately greater than the rise in cardiac output when the hypernatremia is very acute and the blood pressure falls (12–14). The fall in resistance and rise in cardiac output are more proportionate when the hypernatremia is less acute and consequently blood pressure changes very little (15).

According to this analysis, cell hydration in the absence of a fall in blood volume and hence right heart filling pressure should raise blood pressure. Perhaps this explains the rise in blood pressure seen in hypertensive subjects following intravenous infusion of 5% glucose (17). Such an infusion does not lower blood volume (17) but should reduce extracellular osmolality as the glucose is metabolized.

Summary. Blood pressure was measured in anesthetized dogs during acute selective sodium chloride depletion without water depletion; total osmotic pressure of extracellular fluid was held constant thereby preventing osmotic shift of water into cells. The blood pressure changes seen were not different from those in a control series where sodium concentration remained constant. These studies fail to show that acute sodium chloride depletion *per se* affects blood pressure. Apparently the blood pressure changes seen with acute manipulation of the total body sodium chloride content are produced indirectly via associated changes in extracellular osmolality.

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