Effect of a Reduction in Sodium Intake on Cold-Induced Elevation of Blood Pressure in the Rat (43456)

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Abstract. **Chronic exposure of rats to cold (5°C) induces hypertension within 3 weeks. The objective of this study was to determine the effect of treatment with graded levels of dietary NaCl on the induction of hypertension during chronic exposure to cold. Four groups of male rats were used. The first, given a commercial sodium-deficient diet containing 0.30% NaCl, served as the warm-adapted control group. The second, third, and fourth groups were given the same diet containing 0.075%, 0.15%, and 0.30% NaCl, respectively. Because cold-exposed rats ingest approximately twice as much food as warm-adapted controls, this represented half, the same, and twice the amount of NaCl ingested by the control group. The latter three groups were placed in cold air (5°C). All cold-treated groups had an elevation of systolic blood pressure that was proportional to the concentration of NaCl in the diet by the seventeenth week of exposure to cold. Cardiac hypertrophy occurred to the same extent in all cold-exposed groups and was thus unaffected by the NaCl content of the diet or by the extent of elevation of blood pressure. Hence, cardiac hypertrophy during chronic exposure to cold is supported by other factors, possibly by the increased concentration of either norepinephrine or triiodothyronine, or both, which occurs characteristically in rats under these conditions. The results of this experiment suggest that the amount of NaCl ingested daily plays a role in the cold-induced elevation of blood pressure observed in rats.**

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Chronic exposure of laboratory rats to 5°C induces an increase in metabolic rate (1, 2), an elevation in circulating levels of catecholamines (3, 4), and an increase in metabolic responsiveness to norepinephrine and β-adrenergic agonists (5–7). In addition, rats chronically exposed to cold develop the syndrome of hypertension, including cardiac hypertrophy and elevation of systolic, diastolic, and mean blood pressures (8–10). Recent studies have revealed that changes in the baroreceptor reflexes (4) and in the renin-angiotensin-aldosterone system (11) also occur and may contribute to the development of cold-induced hypertension. For example, baroreceptor reflexes are reduced during chronic exposure to cold. This reduces central inhibitory control of sympathetic outflow to the periphery, which results in increased secretion of norepinephrine. Furthermore, chronic treatment with captopril (12), an angiotensin-converting enzyme inhibitor, and spironolactone (13), an aldosterone receptor antagonist, can prevent the cold-induced elevation of blood pressure.

Thus, this type of hypertension is, in some of its characteristics, a naturally occurring analog of hypertension induced experimentally by administration of excessive amounts of a mineralocorticoid hormone (e.g., deoxycorticosterone acetate). Because ingestion of large amounts of NaCl (given as isotonic saline for drinking) is a necessary cofactor in the development of mineralocorticoid-induced hypertension, the aim of the present study was to assess the effect of graded levels of dietary sodium on the development of cold-induced hypertension.

The cold-exposed rat must increase its food con-

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sumption by 50–60% in order to meet the increased energy demand required to offset heat loss to the environment and to maintain body temperature. Hence, the dietary intake of sodium by cold-treated rats is approximately twice that of warm-adapted controls when a commercially available rodent diet is ingested. Epidemiologic studies of many ethnic populations throughout the world have suggested a positive linear relationship between daily intake of sodium and the percentage of the population that is hypertensive (14, 15). Furthermore, a role for sodium is strengthened by the facts that: (i) excessive ingestion can induce hypertension in rats (16), and (ii) strains of rats now exist that become hypertensive when allowed access to NaCl, but do not become hypertensive when access is denied. Furthermore, the fact that diuretics often reduce blood pressure while increasing urinary loss of sodium and chloride offers additional circumstantial evidence for the importance of sodium and chloride in the development and maintenance of hypertension.

Therefore, the objective of the present study was to determine the effect of treatment with graded levels of dietary NaCl on the time-course for induction and the severity of the hypertension that develops during chronic exposure to cold.

Methods

Twenty-five male rats of the Blue Spruce Farms (Sprague-Dawley) strain, approximately 3 months of age and weighing initially from 180 to 200 g, were used. The animals were kept in individual stainless steel cages in temperature (26 ± 2°C)- and light (0700–1900 hr)-controlled rooms. Food (Purina Laboratory Chow No. 5001; Purina Mills, Inc., St. Louis, MO) containing 0.30% NaCl and tap water were provided to the rats *ad libitum*. Fluid containers consisted of infant nursing bottles with cast bronze drinking spouts (17), and food containers were spill resistant (18).

A 2-week control period preceded the experiment. During this time, the systolic blood pressure and body weight of each rat were measured once weekly. Systolic blood pressure measurements were made by the tail-cuff method of Fregly (19) using a NarcoBio Instruments Co. (Houston, TX) polygraph. The average of eight measurements was taken as the mean systolic blood pressure of each rat. During the second week of the control period, the rats were divided into four groups, such that the mean systolic blood pressures of any two groups were not significantly different. One group (n = 6) remained at 26°C and received the Hartroft Sodium Test Diet (No. 902903; United States Biochemical Corp., Cleveland, OH) containing 67% carbohydrate, 20% protein, 2% fat, and 0.30% NaCl by weight. The other three groups were exposed to cold (5 ± 2°C) and received the same diet containing either 0.075% NaCl (n = 6), 0.15% NaCl (n = 6), or 0.30% NaCl (n = 6) by weight. The diets and distilled, deionized water were provided to the rats *ad libitum*.

The animals were allowed 1 week to adjust to the diet prior to placement in the cold. Thereafter, systolic blood pressures and body weights were measured once weekly for 16 weeks. During the first, third, fifth, and eleventh weeks of exposure to cold, food and water intake, as well as urinary outputs, was measured daily for 3 days. Urine was collected in 1.0 ml of 6 N HCl, frozen at −20°C, and stored for later analysis of norepinephrine, creatinine, sodium, and potassium concentrations. Urinary norepinephrine was measured by high pressure liquid chromatography with electrochemical detection (20, 21). Urinary creatinine was measured by the method of Chasson *et al.* (22) using a Technicon Autoanalyzer. Urinary sodium and potassium concentrations were measured by flame photometry (Corning 480; Ciba Corning Diagnostics Corp., Medfield, MA) using lithium as the internal standard.

The dipsogenic responsiveness to acute administration of angiotensin II ([Ang II] human sequence; No. A9525; Sigma Chemical Co., St. Louis, MO) was measured during the seventeenth week of exposure to cold. Prior to administration of Ang II (150 μg/kg, sc), water bottles and food containers were removed from the cages. Each rat was weighed, injected with Ang II, and placed alone in its cage at the room temperature to which it was adapted. A preweighed bottle of distilled, deionized water was placed on each cage. Those rats in the cold received water at 5°C, whereas the controls received water at 26°C. No food was available during the study. Water intake by each rat was measured gravimetrically at 0.5, 1.0, and 2.0 hr after administration of Ang II.

On Day 121 of exposure to cold, all rats were sacrificed by decapitation. Trunk blood was collected in chilled beakers containing either EDTA or no anticoagulant. All samples were immediately placed on ice and centrifuged in the cold. Plasma was removed and frozen at −20°C for later analysis of plasma renin activity (PRA), aldosterone, sodium and potassium concentrations, and osmolality. PRA was measured by means of the New England Nuclear human radioimmunoassay kit (No. 1485; Baxter Healthcare Co., Cambridge, MA). The concentration of aldosterone in plasma was measured by radioimmunoassay (Coat-a-Count Kit, No. TKAL2 254; Diagnostic Products Co., Los Angeles, CA), and the concentrations of sodium and potassium in plasma were measured by flame photometry. Plasma osmolality was measured by vapor pressure osmometry (model 5100C; Wescor Co., Logan, UT). In addition, three microhematocrit tubes were filled with blood collected from the trunk for the determination of hematocrit. At death, the heart, kidneys, thyroid, adrenal glands, and interscapular brown fat pad were removed and cleaned of extraneous tissue

and weighed. The heart was then sectioned into the left and right ventricles, which were weighed separately.

The data for systolic blood pressures, body weights, food and water intakes, urine outputs, and dipsogenic responsiveness to Ang II were analyzed by a repeated-measures one-way analysis of variance. The data for organ weights, PRA, aldosterone, sodium and potassium concentrations, hematocrit, and plasma osmolality were analyzed by a one-way analysis of variance. The post hoc Duncan's new multiple range test was used to test the significance of the difference between two individual means. The level of significance was set at the 95% confidence limit. All data are expressed as the mean ± SE.

Results

The systolic blood pressures of the four groups did not differ during the 2-week control period (Fig. 1A). After exposure to cold, the systolic blood pressures of the four groups diverged. Thus, the group receiving 0.30% NaCl in their diet had a pressure of about 150 mm Hg by Day 112 of exposure to cold, whereas the pressure of the group receiving 0.15% NaCl was about 140 mm Hg and that of the group receiving 0.075% NaCl in their diet was about 130 mm Hg. The systolic blood pressure of the warm-adapted group was about 120 mm Hg. The repeated-measures analysis of variance revealed a significant ($P < 0.001$) effect of treatment (F[3,20] = 100.6), a significant ($P < 0.001$) effect of time (F[13,260] = 44.16), and a significant ($P < 0.001$) treatment × time interaction (F[13,260] = 3.74). The latter suggests that treatments had a significant effect on the rates of elevation of blood pressure among the groups. An assessment of the differences among the groups with respect to the means of the final measurement of systolic blood pressure revealed that the blood pressures of the warm-adapted control group (0.30% NaCl in diet) differed significantly ($P < 0.01$) from those of the cold-treated groups receiving 0.15% and 0.30% NaCl in their diets. Mean systolic blood pressure of the cold-treated group receiving the lowest concentration of NaCl (0.075%) in their diet did not differ significantly from that of the warm-adapted control group.

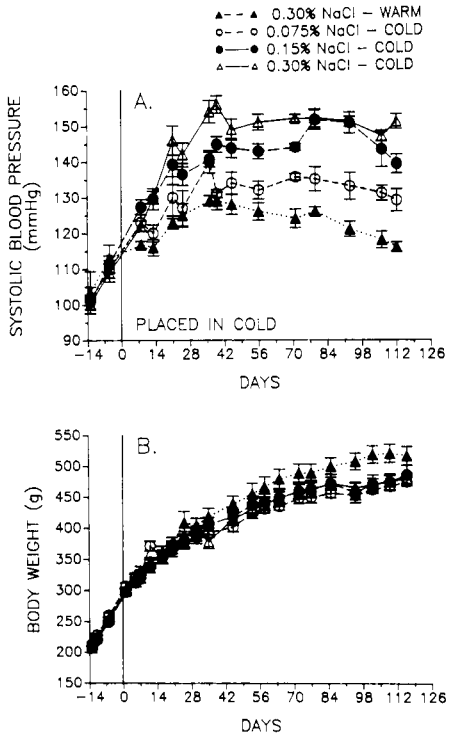

Figure 1. The effect of chronic exposure to cold on (A) systolic blood pressures and (B) body weights of rats treated chronically with graded dietary concentrations of NaCl. The rats were allowed 1 week before placement in cold to adjust to the diets. On Day 0, the rats were placed in cold (5°C). The four groups are designated in the figure. Means ± SE are shown.

The body weights did not differ significantly among all four groups before exposure to cold (Fig. 1B). After exposure to cold, body weight of the warm-adapted control group was higher than that of the cold-treated groups. However, there was no significant effect of cold on body weight (F[3,20] = 1.58), although there was a significant ($P < 0.001$) effect of time (F[21,420] = 1042.46) and a significant ($P < 0.001$) treatment × time interaction (F[63,420] = 3.52). The latter suggests that there were significant differences in the rates of growth among the four groups, with the warm-adapted control group growing at a rate significantly ($P < 0.01$) faster than any of the other three groups.

Food and water intakes, as well as urine outputs, were measured during the control period and during the first, third, fifth, and eleventh weeks of exposure to cold. All cold-treated groups ingested significantly ($P < 0.01$) more food than the warm-adapted group (Fig. 2A). There was no significant difference in intake among the cold-treated groups. The daily sodium intakes were 50% lower (0.075% NaCl diet), the same (0.15% NaCl diet), and 50% higher (0.30% NaCl diet) in the cold-treated groups than in the warm-adapted group receiving 0.30% NaCl in food (Table I). Water intakes, measured during the first week of exposure to cold, were significantly ($P < 0.01$) lower in the cold-treated groups compared with those of the warm-adapted group (Fig. 2B). However, during the third, fifth, and eleventh weeks, the water intakes of the cold-treated and warm-treated groups did not differ, except that the group given 0.075% NaCl in their diet had a significantly ($P < 0.01$) greater water intake during the eleventh week than the warm-adapted group. This is due to the decrease in water intake of the warm-adapted group at this time. The daily urine outputs of the cold-treated groups increased significantly ($P < 0.01$) throughout the study compared with those of the warm-adapted group (Fig. 2C). There were no significant

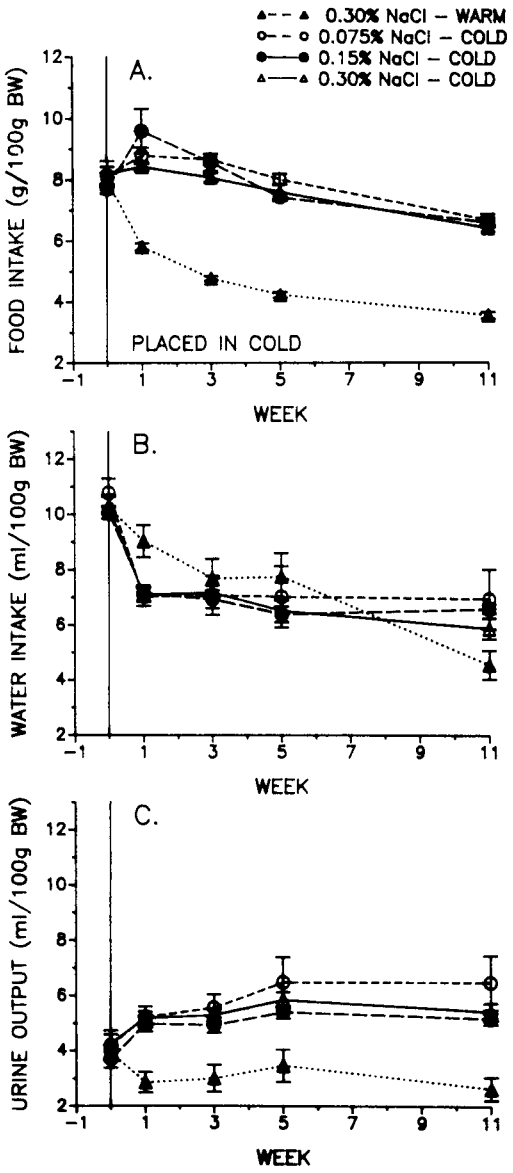

Figure 2. The effect of chronic exposure to cold on the mean daily intakes of (A) food and (B) water as well as (C) the outputs of urine in rats treated chronically with graded dietary levels of NaCl. The four groups are designated in the figure. Means ± SE are shown.

differences in urine outputs among the three cold-treated groups.

Prior to exposure to cold, the groups receiving either 0.075% or 0.15% NaCl in their diets excreted significantly ($P < 0.01$) less sodium in their urine than the two groups receiving 0.30% NaCl in their diet (Fig. 3A). There were no significant differences between the two groups receiving 0.30% NaCl during the control period. During exposure to cold, the daily urinary output of sodium in all cold-treated groups increased significantly ($P < 0.01$) above their pre-cold exposure levels. This increase in output was associated with an increased intake of food. However, there were significant differences among all three cold-treated groups. The cold-treated group given the diet containing 0.30% NaCl excreted about 50% more sodium ($P < 0.01$) than the group given 0.15% NaCl. The group given 0.075% NaCl excreted about 50% less ($P < 0.05$) sodium than the group given 0.15% NaCl. After 11 weeks of exposure to cold, the group given 0.15% NaCl in their food and the warm-adapted group excreted the same amount of sodium in their urine.

During exposure to cold, all cold-treated groups increased their urinary potassium output significantly ($P < 0.01$) compared both with pre-cold exposure values and with the warm-adapted controls (Fig. 3B). There were no significant differences among the three cold-treated groups, except that during the fifth week of exposure to cold, the group receiving 0.15% NaCl excreted less ($P < 0.01$) potassium than the cold-treated group receiving 0.30% NaCl.

The two groups receiving 0.30% NaCl in their diet (cold-treated and warm-adapted groups) excreted the most sodium for a given potassium output (Fig. 3C). There were no significant differences between these two groups, except during the third and fifth weeks of exposure to cold, when the ratio of sodium to potassium of the cold-treated group receiving 0.30% NaCl was increased significantly ($P < 0.05$) compared with those of the warm-adapted group. The ratios of sodium to potassium of the groups receiving 0.075% and 0.15% NaCl were significantly ($P < 0.01$) less compared with those of both groups receiving 0.30% NaCl.

The output of norepinephrine into urine increased significantly ($P < 0.01$) in the three cold-treated groups compared with the warm-adapted control group (Fig. 4). There were no significant differences among the three cold-treated groups.

The dipsogenic responsiveness to acute administration of Ang II in the cold-treated groups receiving 0.15% and 0.30% NaCl in their diet was significantly ($P < 0.05$) greater compared with both the warm-adapted group and the group receiving 0.075% NaCl in their food (Fig. 5). There was no significant difference between the latter two groups.

On Day 121 of exposure to cold, all of the rats in each group were sacrificed. The weights of the whole heart, left ventricle, kidneys, and brown fat were significantly ($P < 0.05$) increased in the cold-treated groups compared with those of the warm-adapted group (Fig. 6). There was no significant difference in the weight of these organs among the cold-treated groups, except for brown fat. The weight of the brown fat of the rats given 0.075% NaCl in their diet was significantly ($P < 0.01$) less than those of the other two cold-treated groups. The weights of the right ventricle and the thyroid gland did not differ among all four groups. There were also no significant differences in the weight of the adrenal glands among the four groups; therefore, the data are not shown.

Table I. Effect of Chronic Exposure to Cold on Mean Daily Sodium Intake (mg/100 g body wt)[a]

Group	Week 0	Week 1	Week 3	Week 5	Week 11
0.30% NaCl + warm	24.0 ± 0.8	20.0 ± 0.1	14.0 ± 0.2	13.0 ± 0.3	10.0 ± 0.4
0.075% NaCl + cold	16.0 ± 0.4[b]	7.0 ± 0.4[b]	7.0 ± 0.2[b]	6.0 ± 0.1[b]	5.0 ± 0.1[b]
0.15% NaCl + cold	12.0 ± 0.2[b]	15.0 ± 1.1[c]	13.0 ± 0.3[b]	11.0 ± 0.3	10.0 ± 0.3
0.30% NaCl + cold	24.0 ± 0.9	27.0 ± 0.2[b]	24.0 ± 0.4[b]	23.0 ± 0.8[b]	19.0 ± 0.4[c]

[a] Data shown are means ± 1 SE.
[b] $P < 0.01$ compared with group receiving 0.30% NaCl + warm.
[c] $P < 0.05$ compared with group receiving 0.30% NaCl + warm.

PRA, the concentrations of aldosterone, sodium and potassium in plasma, and osmolality of the plasma did not differ among all four groups. In addition, no significant differences in hematocrit were found (Table II).

Discussion

Chronic exposure to cold induced a significant elevation of systolic blood pressure (Fig. 1A). The extent of elevation was dependent upon the concentration of NaCl in the diet. This suggests that the amount of NaCl ingested daily plays a role in the cold-induced elevation of blood pressure. Other studies from this laboratory have identified additional factors that can influence the cold-induced elevation of blood pressure. These include: (i) the initial body weight at the time of exposure to cold (23); (ii) the number of days and the amount of time each day the rat is exposed to cold (23); and (iii) the ambient temperature (23). An additional factor may include the strain of rats used, because recent studies have shown that the Long-Evans (Hooded) strain does not develop as severe an elevation of blood pressure during chronic exposure to cold as do rats of the Sprague-Dawley strain (24).

All cold-treated groups showed an increase in the weight of the whole heart, which was due in large part to an increase in the weight of the left ventricle (Fig. 6) (10, 12, 23). The left ventricle is the chamber of the heart most affected by an increase in peripheral vascular resistance. This provides additional evidence that chronically cold-exposed rats are hypertensive. However, it is surprising that the groups that failed to have an elevation of blood pressure had hypertrophied hearts. We have also observed this in other studies in which the cold-induced elevation of blood pressure was prevented by chronic treatment with either captopril, an angiotensin I-converting enzyme inhibitor, or spironolactone, an aldosterone receptor antagonist (12, 13). The persistent hypertrophy of the heart may have been induced by the increased concentration of norepinephrine in the plasma of the cold-treated rats (3, 4). Cardiac hypertrophy can be induced in the rat by chronic administration of norepinephrine (25), epinephrine (26), and isoproterenol, a synthetic β-adrenoceptor agonist (27). In addition, chronic administration of L-thyroxine to rats also results in increased weights of the heart and interscapular brown fat (28, 29). During chronic exposure to cold, the concentrations of thyroid-stimulating hormone and triiodothyronine in serum are increased (28). The source of the triiodothyronine appears to be L-thyroxine, which is monodeiodinated by peripheral organs, especially the liver and kidneys (28). Hence, an increased concentration of triiodothyronine in plasma during chronic exposure to cold may contribute, either alone or in combination with norepinephrine, to the persistent cardiac hypertrophy observed in the present and previous studies.

The mechanism(s) by which hypertension is induced in rats during exposure to cold is not known with certainty. Recent studies from this laboratory have shown a reduced sensitivity of the baroreceptor reflexes in chronically cold-exposed rats (4). This would be expected to result in reduced inhibitory control of central sympathetic outflow to the periphery and an increased secretion of norepinephrine. Since elevated concentrations of norepinephrine in plasma can stimulate the secretion of renin from the kidneys and the subsequent formation of Ang II, the hypertension induced by exposure to cold in rats is most likely caused by this potent vasoconstrictor agent. Indeed, we have been able to prevent the elevation of blood pressure in cold-treated rats by chronic treatment with captopril, clonidine, or spironolactone, all of which can interfere with the renin-angiotensin-aldosterone system at different levels (12, 13).

A previous study from this laboratory reported an activation of the renin-angiotensin system, as assessed by an elevation in PRA during the first 2 weeks that rats were exposed to cold (11). However, after 4 weeks of exposure to cold, PRA was reduced significantly below the level of the warm-adapted controls. At this time, both blood pressure and dipsogenic responsiveness to Ang II increased. The latter was interpreted as suggesting an up-regulation of Ang II receptors, particularly those in the brain, where the drinking response is apparently mediated (11, 30). When the data for all groups were used, there was a significant negative linear relationship between water intake after administration of Ang II and PRA (11). This would be expected if the

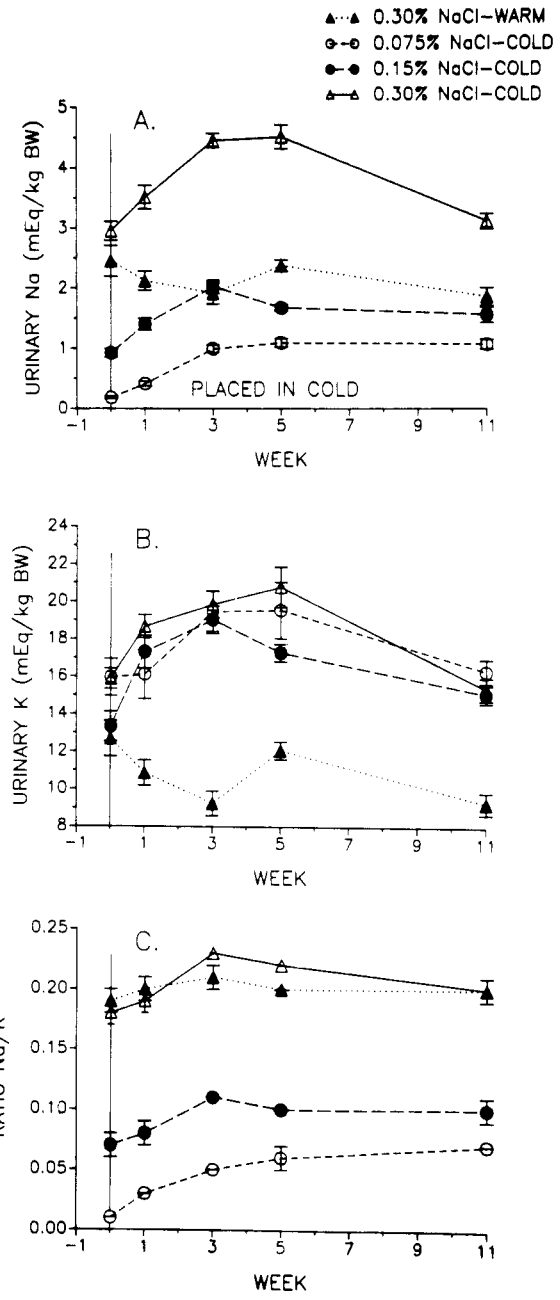

Figure 3. The effect of chronic exposure to cold on the mean daily urinary outputs of (A) sodium and (B) potassium, and the ratio of (C) sodium to potassium is shown for the four groups identified in the figure. Means ± SE are shown.

concentration of Ang II in plasma regulated its own receptors.

The results of the present experiment indicate that the PRA of two of the three cold-treated groups was reduced below that of the warm-adapted control group after 121 days of exposure to cold, but the variability of this measurement precluded statistical significance (Table II). As expected, the concentration of aldosterone in plasma decreased when the cold-treated rats ingested the diet containing the highest concentration

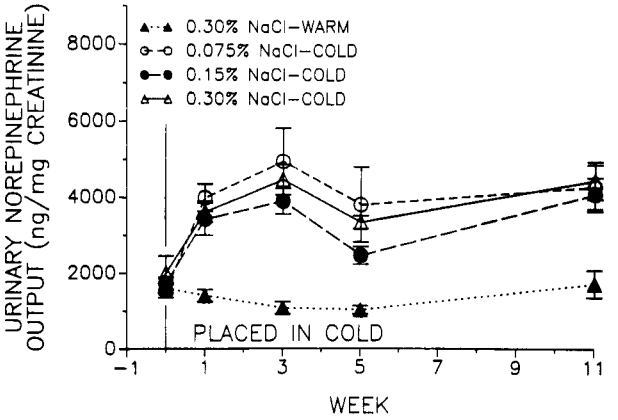

Figure 4. Daily urinary outputs of norepinephrine are shown for the four groups designated in the figure. Means ± SE are shown.

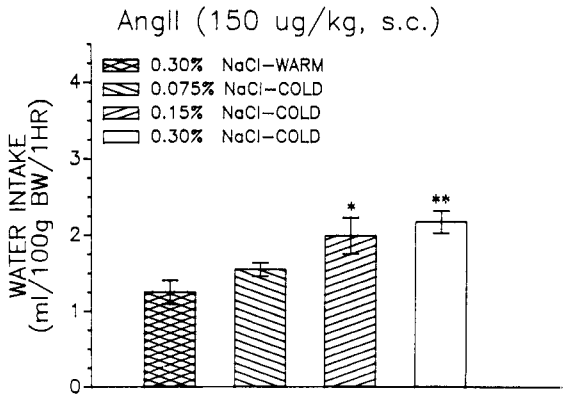

Figure 5. Water intakes of the warm-adapted and cold-treated groups 2 hr after administration of angiotensin II (150 μg/kg, sc) are shown. The groups are identified in the figure. Means ± SE are shown. $^*P < 0.05$; $^{**}P < 0.01$ compared with the warm-adapted group.

of NaCl; however, the large variability of this measurement again precluded statistical significance (Table II).

During the seventh week of the present experiment, the dipsogenic responsiveness to Ang II was tested. Increased responsiveness was observed in cold-treated groups ingesting the two higher concentrations of NaCl in their diets compared with the warm-adapted control group (Fig. 5). The results are consistent with an up-regulation of Ang II receptors, as discussed above. Furthermore, the state of the receptors for Ang II in the diencephalon of rats is known to be correlated directly with the dipsogenic responsiveness to Ang II, whether administered either centrally or peripherally (30). In addition, several studies suggest a direct correlation between the state of receptors for Ang II in the diencephalon and the development of hypertension; i.e., up-regulation of receptors for Ang II has been linked to the inductions of both deoxycorticosterone acetate-salt and spontaneously induced hypertensions (30–33). The results of the present study are at least consistent with an up-regulation of central Ang II receptors in the cold-

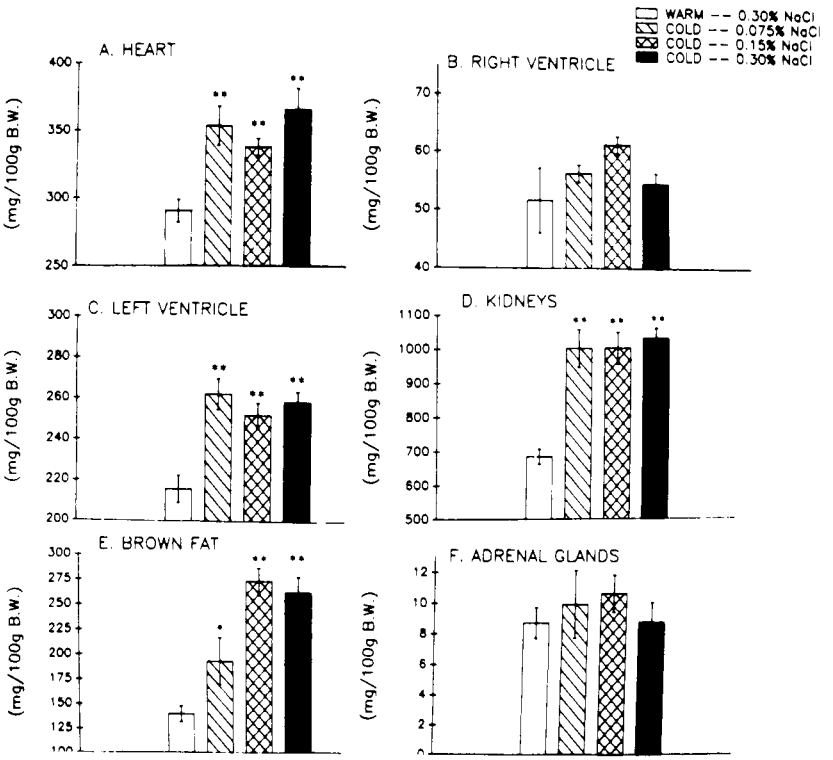

Figure 6. Organ weights, including (A) heart, (B) left ventricle, (C) right ventricle, (D) thyroid gland, (E) kidneys, and (F) interscapular brown fat pad are shown for the four groups identified in the figure. Means ± SE are shown. $^{*}P < 0.05$; $^{**}P < 0.01$ compared with the warm-adapted control group.

Table II. Effect of Chronic Exposure to Cold and Dietary Sodium Intake on Hematocrit, Serum Electrolytes, Plasma Aldosterone Concentration, and Plasma Renin Activity[a]

Group	Hematocrit	Na (mEq/liter)	K (mEq/liter)	Osmolality (mOsm/kg)	PRA (ng/ml/hr)	Aldosterone (pg/ml)
0.30% NaCl + warm	47.5 ± 0.9	151.4 ± 2.0	7.5 ± 0.1	312 ± 6	4.1 ± 0.6	65.7 ± 22.1
0.075% NaCl + cold	47.5 ± 0.5	152.4 ± 3.8	8.0 ± 0.2	317 ± 10	5.0 ± 0.9	55.6 ± 19.2
0.15% NaCl + cold	48.6 ± 0.5	145.4 ± 5.1	7.5 ± 0.3	296 ± 12	3.7 ± 0.7	61.0 ± 18.3
0.30% NaCl + cold	46.8 ± 0.9	148.2 ± 0.9	7.8 ± 0.2	314 ± 4	2.9 ± 0.5	31.9 ± 7.3

[a] Data shown are means ± 1 SE.

treated groups on the diets containing 0.15% and 0.30% NaCl.

Chronic exposure to cold characteristically increases food intake, urine output, and urinary norepinephrine excretion in rats (3, 7, 34). Variation in dietary intake of sodium had no significant effect on any of these. Since urinary output of norepinephrine reflects plasma concentration, the results suggest that the elevated blood pressure observed during exposure to cold is not related solely to the increased level of norepinephrine in plasma (10). The more likely role of norepinephrine during exposure to cold is in the maintenance of heat production and body temperature (3, 5).

Chronic exposure to cold also characteristically increases the weight of the kidneys (10, 12, 13). Variation in the level of NaCl in the diet had no significant additional effect. The increased consumption of food accompanying exposure to cold, with the consequent increase in excretion of metabolites, is likely to be responsible for induction of renal hypertrophy.

The results of this and earlier studies suggest that the hypertension induced by exposure to cold is a naturally occurring analog of the mineralocorticoid-salt-induced hypertension produced in the laboratory. Thus, there appears to be an increased secretion of Ang II within the first few weeks of exposure to cold which apparently initiates the elevation of blood pressure (11). As the secretion of Ang II decreases, the dipsogenic responsiveness to administration of Ang II increases, which suggests an up-regulation of receptors for Ang II. The involvement of the renin-angiotensin-aldosterone system in the development of cold-induced hyperten-

sion is further suggested by the fact that chronic administration of captopril, spironolactone, or clonidine, which inhibit the renin-angiotensin-aldosterone system at different levels, can either prevent or ameliorate the development of hypertension (12, 13). The present study adds to these observations by documenting a role for the NaCl content of the diet in the development of cold-induced hypertension, as has been observed previously for mineralocorticoid-induced hypertension.

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