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# Changes in Blood Pressure and Dipsogenic Responsiveness to Angiotensin II During Chronic Exposure of Rats to Cold[1]

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FREGLY, M. J., O. SHECHTMAN, P. VAN BERGEN, C. REEBER AND P. E. PAPANEK. *Changes in blood pressure and dipsogenic responsiveness to angiotensin II during chronic exposure of rats to cold.* PHARMACOL BIOCHEM BEHAV **38**(4) 837–842, 1991.—Hypertension accompanies chronic exposure of rats to cold (5–6°C). Systolic, diastolic, and mean blood pressures become elevated, and hypertrophy of the heart occurs. A previous study from this laboratory suggested that the renin-angiotensin system may play a role. The present study was carried out to assess this further. Thus, in addition to measurement of systolic blood pressure at intervals during exposure to cold, plasma renin activity and the dipsogenic responsiveness to acute administration of angiotensin II were also measured to assess the functional status of the renin-angiotensin system. The results showed a significant ($p<0.05$) increase in systolic blood pressure during the third week of exposure to cold. In contrast, plasma renin activity (PRA) increased within the first week of exposure to cold, and declined thereafter to reach the level of the control by the third week of exposure to cold. By the fourth week, PRA decreased to a level significantly ($p<0.05$) below that of the control group. The responsiveness to acute administration of angiotensin II (AII), as assessed by the drinking response, increased significantly ($p<0.05$) by the third week of exposure to cold and remained significantly elevated during the fourth week. There was a significant ($p<0.01$) direct relationship between dipsogenic responsiveness to AII and blood pressure in the cold-treated ($r=.57$), but not the control group ($r=.12$). There was also a significant ($r=-.91$) indirect linear relationship between PRA and dipsogenic responsiveness to AII. Cold-treated rats had significant increases in urinary norepinephrine output and weights of heart, kidneys, adrenals, and brown adipose tissue characteristic of rats acclimated to cold. Thus, the results suggest, but do not prove, either that the elevation of blood pressure under these conditions may be induced by changes in the renin-angiotensin system or that the same mechanism(s) affects both functions. The results suggest further that the reduction in the drinking response to AII accompanying increases in plasma renin activity may be related to changes in the regulation of central receptors for AII.

Cold exposure Cold-induced hypertension Renin-angiotensin system Plasma renin activity Angiotensin II-induced drinking

WHEN rats are exposed to a cold environment, they develop hypertension, including an elevation in mean blood pressure and cardiac hypertrophy, within 3 to 4 weeks of exposure to cold (4, 9, 10, 30). Exposure to cold also induces both an elevation in the circulating levels of catecholamines (22) and the metabolic responsiveness to them, particularly beta-adrenergic catecholamines (1, 7, 8, 21). Stimulation of the beta-adrenergic receptors in the kidneys increases release of renin (28,34) which, in turn, contributes to the production of angiotensin II (AII), a potent vasoconstrictor agent. Thus it is possible that an increase in the production of AII might be involved in the induction of hypertension during exposure to cold. This suggestion is based on results of a recent study which showed that captopril, an angiotensin I (AI) converting enzyme inhibitor, prevented the elevation of blood pressure in rats exposed to cold (31). However, interpretation of the results is complicated by the fact that captopril does have alpha$_1$-adrenergic inhibitory activity (16, 18, 19, 25). Further, inhibition of the AI converting enzyme increases the half-life of bradykinin, a peptide known to decrease vascular resistance (29), and inhibits plasma enkephalinase, a peptidase capable of degrading enkepha-

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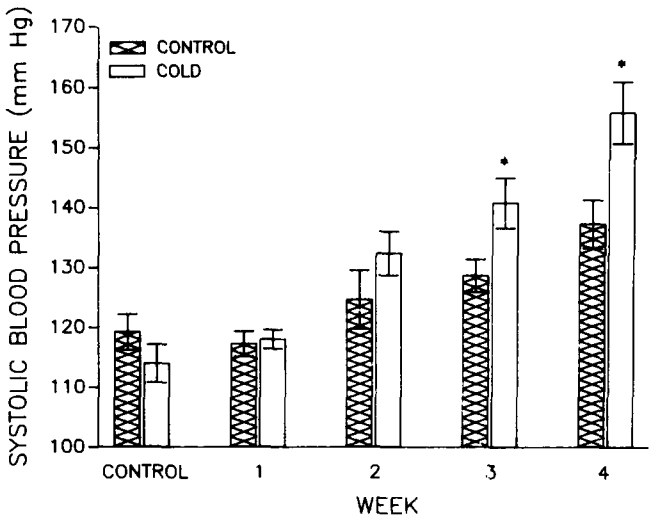


FIG. 1. Systolic blood pressure of control and cold-treated groups of rats prior to exposure to cold and at weekly intervals thereafter for 4 weeks. The groups are identified in the figure. One standard error is set off at each mean. *$p<0.05$ compared to control group.

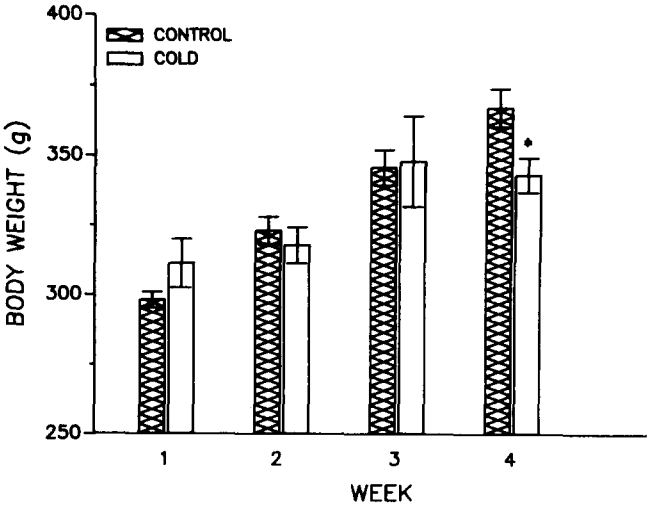


FIG. 2. Mean body weights of the two groups shown in Fig. 1 during the course of the experiment. One standard error is set off at each mean. *$p<0.05$ compared to control group.

lins (12, 17, 23). Thus the diversity of effects of captopril makes it difficult to know the contribution of each in the prevention of cold-induced hypertension.

Thus the aim of the present study was to assess the status of the renin-angiotensin system of cold-treated rats, including responsiveness to acute administration of AII, as measured by its effect on drinking. These measurements were carried out at weekly intervals during 4 weeks of exposure to cold.

## METHOD

Thirty male rats of the Sprague-Dawley (Blue Spruce Farms) strain weighing initially from 200 to 250 g were used. A two-week control period preceded the experiment. During this time, the systolic blood pressures and body weights of each rat were measured weekly. At the end of this time, the rats were divided randomly into 5 equal groups. The rats were housed individually in temperature-controlled rooms at either $26\pm2$°C ($n=6$) or $5\pm2$°C ($n=24$). The rooms were illuminated from 7 a.m. to 7 p.m. daily. All rats were provided with finely powdered Purina Laboratory Chow (#5001) and tap water ad lib. Fluid containers consisted of infant nursing bottles with cast bronze drinking spouts (20), and food containers were spill resistant (5). Systolic blood pressures of the rats were measured weekly by the method of Fregly (6), modified for use with a NarcoBio Instruments Co. polygraph. Urinary norepinephrine concentrations were measured by high pressure liquid chromatography with electrochemical detection as described earlier (3,15). Plasma renin activity (PRA) was measured by means of the New England Nuclear human RIA kit.

Six cold-treated rats were sacrificed by decapitation one week after exposure to cold and every week thereafter. During the fourth week, the control group was sacrificed as well. Trunk blood was collected in chilled beakers containing EDTA, placed immediately on ice, and centrifuged in the cold. Plasma was removed and frozen at −20°C for later analysis of PRA. At death, the heart, kidneys, adrenal glands, and interscapular brown fat pad (IBFP) were removed, cleaned of extraneous tissue and weighed. The heart was sectioned into the left ventricle, right ventricle, and atria and weighed.

At the beginning of each week, water and food intakes, as well as urine outputs, were measured daily for 3 days in the cold-treated rats to be sacrificed and in the warm-adapted controls. In addition, the water intake, induced by acute administration of AII, was also measured. Each rat was weighed and placed alone in a metabolic cage without food. Cold-treated rats remained in the cold, while control rats remained at 26°C. Each rat was administered AII (150 μg/kg, SC, Sigma A9595). The temperature of the water provided to the cold-treated group was 5°C, while that of the water provided to the controls was 26°C. Water intake was measured during the first hour after treatment. Systolic blood pressures and body weights of both cold-treated and control groups were measured one day prior to sacrifice.

The data for food and water intakes, urine output, and the dipsogenic responsiveness to AII were analyzed by a repeated measures one-way ANOVA. The data for blood pressures, body weights, organ weights, PRA and norepinephrine output into urine were analyzed by a one-way ANOVA using the Newman-Keuls procedure to assess the significance of differences between two means. Significance was set at the 95% confidence limit.

## RESULTS

Systolic blood pressures of both cold-treated and control groups increased during the 4 weeks of exposure to cold (Fig. 1). By the third week, blood pressure of the cold-treated group was significantly greater than that of controls ($p<0.05$). The difference was more pronounced during the fourth week of the experiment ($p<0.02$).

Body weight of the cold-treated group was not different from that of the warm-adapted control group until the fourth week of the experiment, at which time it was significantly ($p<0.05$) less (Fig. 2).

The dipsogenic responsiveness to acute administration of AII was greater in the cold-treated group than control during the last 3 weeks of the experiment (Fig. 3). However, the difference between groups was significant ($p<0.01$) only during the third and fourth weeks. There was a significant direct relationship between

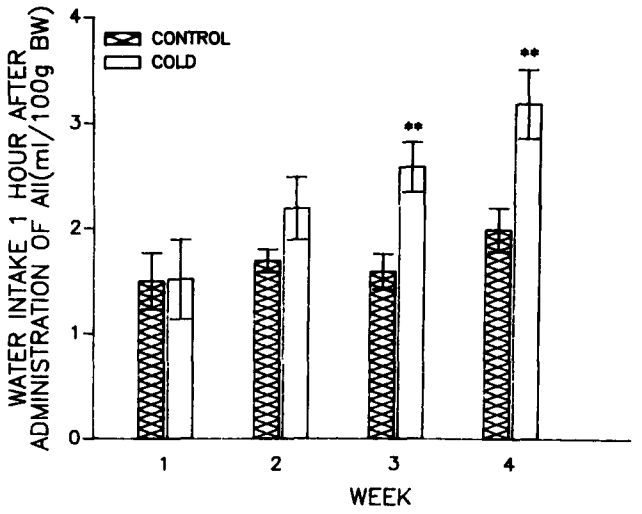


FIG. 3. Water intakes of control and cold-treated groups one hour after administration of angiotensin II (150 μg/kg, SC). The groups are identified in the figure. One standard error is set off at each mean. $^{**}p<0.01$ compared to control group.

systolic blood pressure of each cold-treated rat and its dipsogenic responsiveness to acute administration of AII ($Y = 0.03X - 1.7$; $r = .57$; $p<0.01$) (Fig. 4). However, this relationship was not significant in the control group ($Y = -0.006X + 2.53$; $r = .12$; $p>0.05$).

Daily food and water intakes, as well as urine outputs, of the cold-treated group were significantly ($p<0.01$) greater than those of warm-adapted controls throughout the experiment (Fig. 5A,B,C).

Urinary output of norepinephrine by the cold-treated group was significantly ($p<0.01$) greater than that of the warm-adapted control group throughout the experiment (Fig. 6). However, there

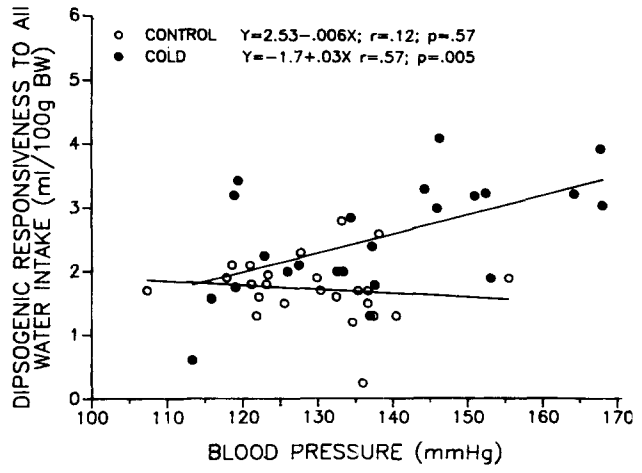


FIG. 4. Dipsogenic responsiveness to angiotensin II (150 μg/kg, SC; 1 hour water intake) is graphed against the systolic blood pressure of each rat measured one day prior to administration of angiotensin II. The groups are identified in the figure. The equations, correlation coefficients (r), and probability ($p$) values of the relationship for control and cold-treated groups are given.

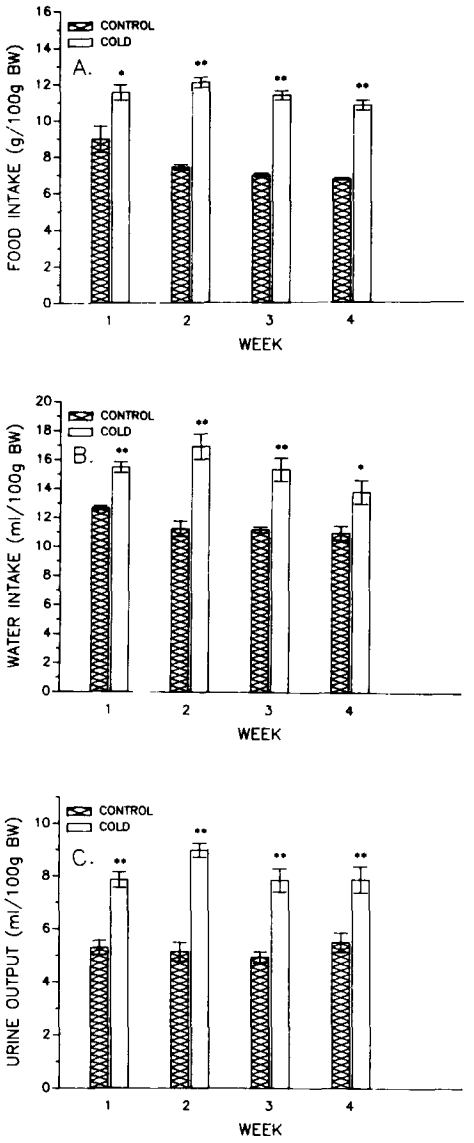


FIG. 5. Mean daily intakes of food (A) and water (B) and output of urine (C) are shown for control and cold-treated rats during each week of the experiment. The groups are designated in the figure. One standard error is set off at each mean. $^{*}p<0.05$; $^{**}p<0.01$ compared to control group.

was a steady decline in the norepinephrine output of the cold-treated group with increasing time of exposure to cold. A decline of 36% from the maximum occurred by the end of the fourth week of exposure to cold.

When measured at death, the weight of the heart had increased significantly ($p<0.01$) above that of warm-adapted controls within the first week of exposure to cold and remained significantly ($p<0.01$) elevated thereafter (Table 1). The weight of the left ventricle also increased significantly ($p<0.01$) above that of warm-adapted controls within the second week of the experiment and remained significantly ($p<0.01$) elevated thereafter. There were no significant changes in the weights of the right ventricle and atria induced by exposure to cold at any time during the experiment. The weights of kidneys, adrenal glands, and interscapular brown fat pad (IBFP) of the cold-treated groups were increased significantly ($p<0.01$) above that of the warm-adapted control

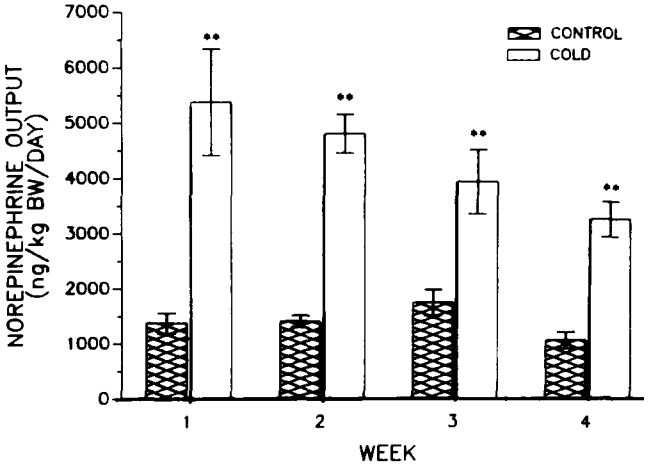


FIG. 6. The output of norepinephrine into urine is shown for the two groups during the four weeks of the experiment. One standard error is set off at each mean. $^{**}p<0.01$ compared to control group.

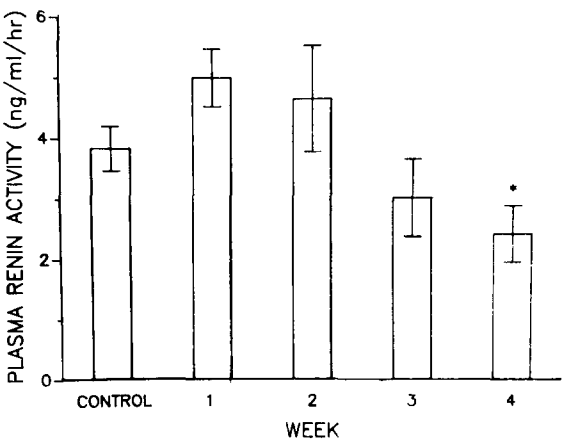


FIG. 7. Plasma renin activity is shown throughout the experiment. Control group was not exposed to cold. One standard error is set off at each mean. $^{*}p<0.05$ compared to control group.

group at all four weeks of the experiment (Table 1).

Plasma renin activity (PRA) increased during the first week of the experiment and declined gradually thereafter to reach a level significantly ($p<0.05$) below that observed in the warm-adapted control group (Fig. 7).

The relationship between PRA and water intake after administration of AII is shown in Fig. 8. The relationship was significant ($r=-.91$; $p<0.01$) and indirect. Thus, as PRA increased, the dipsogenic response to administration of AII decreased.

The relationship between urinary output of norepinephrine and PRA was also assessed (Fig. 9). In this case there was a significant ($p<0.01$) direct relationship between the two variables. Thus, as urinary output (and presumably secretion) of norepinephrine increased, PRA increased.

## DISCUSSION

As we have reported in previous publications, cold-treated rats had a significant elevation in their blood pressure within 3 to 4 weeks of chronic exposure to cold (4, 9, 10, 30). The mechanism(s) for induction of hypertension following chronic exposure to cold is incompletely understood, and is presently under study. However, recent studies have implicated the renin-angiotensin system (RAS) as a contributor since chronic treatment with the angiotensin I converting enzyme inhibitor, captopril, prevented the elevation of blood pressure in cold-treated rats (31). The results of the present experiment support a role for the RAS in the development of cold-induced hypertension in that PRA increased maximally during the first week of exposure to cold and then gradually declined to reach control level by the third week of exposure to cold (Fig. 7). It is of interest that this is the time (week 3) that systolic blood pressure began to increase (Fig. 1). This suggests that increased secretory activity of the RAA system is induced during the initial period of exposure to cold. This may be an initiating factor in the development of cold-induced hypertension. The fact that PRA declined, and reached a level significantly below that of the warm-adapted control group by the fourth week of exposure to cold suggests that increased secretory activity of the RAA system may initiate, but does not maintain, the elevated blood pressure.

The physiological effects of hormones on the body reflect not only their concentration in blood, but also the responsiveness or sensitivity of tissues to them. Increases in the latter can compen-

TABLE 1

THE EFFECT OF A FOUR-WEEK EXPOSURE TO COLD ON ORGAN TO BODY WEIGHT RATIO (mg/100 g b.wt.) OF CERTAIN ORGANS OF COLD-TREATED AND CONTROL RATS

| | | Cold-Treated | | | |
|---|---|---|---|---|---|
| Organ | Control | Week 1 | Week 2 | Week 3 | Week 4 |
| Heart | 326 ± 7[a] | 362 ± 8† | 372 ± 8† | 377 ± 5† | 376 ± 8† |
| Left Vent. | 221 ± 4 | 234 ± 2 | 245 ± 8† | 256 ± 2† | 256 ± 6† |
| Right Vent. | 64 ± 2 | 65 ± 3 | 68 ± 3 | 68 ± 3 | 73 ± 2 |
| Atria | 28 ± 1 | 37 ± 5 | 32 ± 1 | 34 ± 5 | 36 ± 1 |
| Kidneys | 765 ± 19 | 966 ± 19† | 974 ± 30† | 1027 ± 17† | 914 ± 55† |
| Adrenals | 11 ± 0.4 | 16 ± 0.7* | 15 ± 1* | 15 ± 0.8* | 15 ± 1* |
| IBFP | 61 ± 7 | 159 ± 8† | 195 ± 6† | 203 ± 15† | 198 ± 12† |

[a]Mean ± 1 SE.

*Significantly different from control ($p<0.05$).

†Significantly different from control ($p<0.01$).

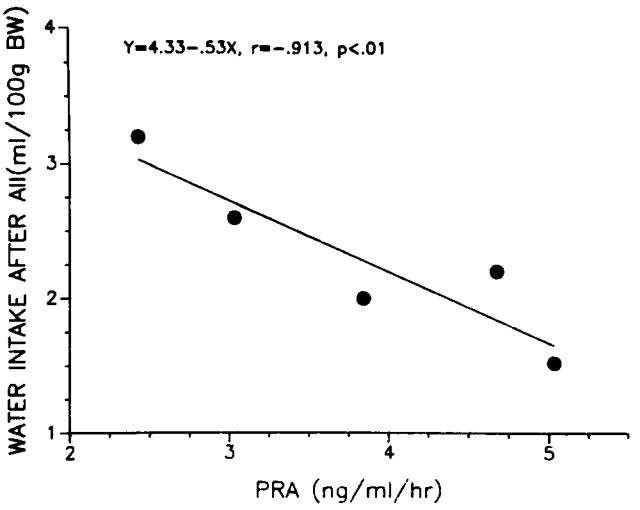


FIG. 8. The relationship between water intake at one hour after administration of angiotensin II (150 μg/kg, SC) and plasma renin activity throughout the experiment. The equation, correlation coefficient (r), and probability value ($p$) for the relationship are shown in the figure.

sate for decreases in the former. To assess the latter, the dipsogenic responsiveness to AII was measured weekly during the 4 weeks of the experiment. By the third and fourth weeks of exposure to cold, dipsogenic responsiveness of the cold-treated group to administration of AII had increased significantly above that of the warm-treated control group (Fig. 3). The state of receptors for AII in the diencephalon of rats is now known to be correlated directly with the dipsogenic responsiveness to AII, whether administered peripherally or centrally (26,27). Further, recent studies (13, 14, 26, 33) also suggest that there is a direct correlation between the state of receptors for AII in the diencephalon and the development of hypertension; i.e., up-regulation of receptors for AII has been linked to the induction of both DOCA-salt and spontaneously induced (SHR) hypertensions. Although we have not

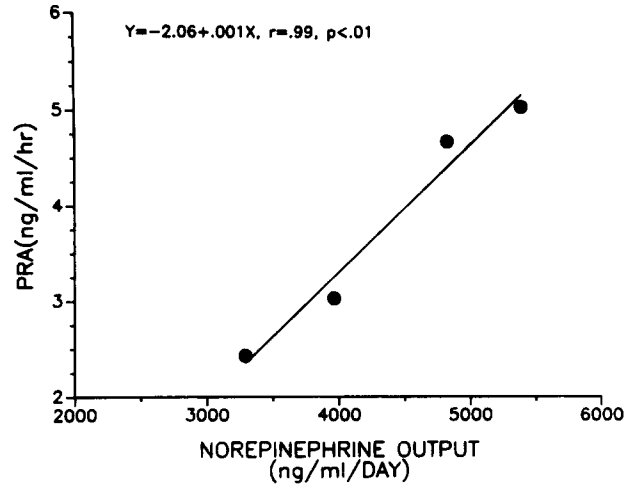


FIG. 9. The relationship between urinary output of norepinephrine and plasma renin activity (PRA) is shown during the four weeks of exposure to cold. The equation, correlation coefficient (r), and probability value ($p$) for the relationship are shown in the figure.

studied the state of central AII receptors in cold-treated rats during chronic exposure to cold, the present results suggest that, after the first two weeks of exposure to cold, both the increased dipsogenic responsiveness to AII and the elevation of blood pressure may be linked to up-regulation of central AII receptors. This possibility is supported by the fact that as PRA was decreasing, dipsogenic responsiveness to AII was increasing. This could exemplify the classic ligand-receptor relationship in which the number of receptors for a given ligand is inversely related to the concentration of the ligand in plasma. Such a relationship between PRA and dipsogenic responsiveness to AII was observed in this experiment (Fig. 8).

Urinary output of norepinephrine increased strikingly during the first week of exposure to cold and remained significantly elevated above the level of the control group throughout the experiment (Fig. 6). These observations confirm those reported previously by others and by this laboratory (22,30). The increased production and excretion of norepinephrine are most likely related to its role in maintaining heat production and body temperature of cold-exposed rats (1, 21, 22). It is unlikely to be directly responsible for elevation of blood pressure in the cold-treated group for a number of reasons. First, both the responsiveness in vivo and the reactivity of vascular smooth muscle in vitro to administration of graded doses of an $alpha_1$-adrenergic agonist (phenylephrine) are reduced in cold-treated rats to levels significantly below those of warm-adapted controls (2,7). This may possibly occur as a result of down-regulation of $alpha_1$-adrenoceptors due to the continued increase in the concentration of norepinephrine in the plasma of cold-treated rats (22). Secondly, treatment of cold-exposed rats with captopril prevented the elevation of their blood pressure, but did not affect the characteristic increase in urinary output (and secretion) of norepinephrine (3, 22, 30). Thirdly, the elevated blood pressure of rats exposed to cold for 5 weeks required about 4 weeks to return to control level after removal from cold (30). In contrast, their increased urinary output of norepinephrine decreased to the level of the control group within 3 days after removal from cold. Hence, increased secretion of norepinephrine could not have been sustaining the elevation of blood pressure under these two conditions.

The results of this study reveal a significant increase in the weight of the heart of the cold-treated group (Table 1). This was due to an increase in the weight of the left ventricle since the weights of the right ventricle and atria were not increased significantly. This provides additional evidence that chronic exposure to cold induces hypertension in rats. Cold-exposed rats also showed a characteristic increase in the weight of the kidneys (9, 10, 30). The increased weight of the kidneys under these conditions has been attributed to the increased food intake accompanying exposure to cold and its consequent increase in excretion of metabolites and electrolytes (30). The increase in the weight of interscapular brown adipose tissue of the cold-treated group is observed characteristically in rats exposed chronically to cold (2,30). Brown adipose tissue is important for nonshivering thermogenesis during exposure to cold (24).

In view of the findings reported here, we suggest that the following mechanism may explain the induction of hypertension during chronic exposure to cold. During the initial stage, an increase in the activity of the sympathetic nervous system occurs. As a result, the concentration of norepinephrine in blood increases, along with an increase in urinary output of norepinephrine. The increased concentration of norepinephrine in plasma manifests itself in many ways in addition to its important role in mobilizing lipid substrate and increasing heat production. Thus it induces vasoconstriction to reduce heat loss. In addition, it also increases the secretion of renin (28,34), the enzyme responsible for the cleavage of AI from angiotensinogen (Fig. 9). It is this

indirect effect of the increased concentration of norepinephrine in plasma, induced by exposure to cold, that may be responsible for the increased rate of release of renin; increased formation of AII, and the eventual elevation of blood pressure. Further, a possibility exists that the elevated levels of both norepinephrine and AII in plasma interact to affect blood pressure and/or that increases in plasma concentration of norepinephrine interact with increases in aldosterone induced by AII to affect blood pressure (27). After about two weeks of elevation in PRA, its level declines at the time blood pressure begins to increase. At this time, the responsiveness to administered AII also increases, suggesting that AII receptors in the diencephalon may be upregulated. The indirect linear relationship between PRA and dipsogenic responsiveness to AII shown in Fig. 8 supports this suggestion. Upregulation of the receptors for AII may sustain the elevated blood pressure during exposure to cold. While this can be considered only an hypothesis at present, the results of the present study are at least consistent with this hypothesis. Additional study will be required either to accept or reject the hypothesis.

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