Factors Affecting Cold-Induced Hypertension in Rats (43156)

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Abstract. **A 3- to 4-week exposure of rats to a cold environment (5 ± 2°C) induces hypertension, including elevation of systolic, diastolic, and mean blood pressures and cardiac (left ventricular) hypertrophy. The studies described here were designed to investigate some factors affecting both the magnitude and the time course for development of cold-induced hypertension. The objective of the first study was to determine whether there was an ambient temperature at which the cold-induced elevation of blood pressure did not occur. The objective of the second experiment was to determine whether body weight at the time of exposure to cold affected the magnitude and time course for development of hypertension. To assess the first objective, male rats were housed in a chamber whose temperature was maintained at 5 ± 2°C while others were housed in an identical chamber at 9 ± 2°C. After 7 days of exposure to cold, the rats exposed to the colder temperature had a significant elevation of blood pressure (140 ± 2 mm Hg) compared with the group maintained at 9°C (122 ± 3 mm Hg). The rats exposed to 9°C had no significant elevation of systolic blood pressure at either 27 or 40 days after initiation of exposure to cold. At the latter time, the temperature in the second chamber was reduced to 5 ± 2°C. By the 25th day of exposure to this ambient temperature, the rats had a significant increase in systolic blood pressure above their levels at 9°C. Thus, there appears to be a threshold ambient temperature for elevation of blood pressure during exposure to cold. That temperature appears to lie somewhere between 5 and 9°C. The second objective was assessed by placing rats varying in weight from approximately 250 to 430 g in air at 5°C. There was a highly significant direct relationship (r = 0.96) between body weight at the time of introduction to cold and the number of days required to increase systolic blood pressure by 10 mm Hg above pre-cold exposure level. The third objective was to make an initial assessment of potential differences among strains of rats with respect to development of cold-induced hypertension. To this end, rats of the Fischer 344 strain were used. Systolic blood pressures of these rats also increased during chronic exposure to cold. Thus, both ambient temperature and body weight are important factors in the induction of hypertension in cold-treated rats. Furthermore, the development of cold-induced hypertension does not appear to be the function of a specific strain of rats. Hence, chronic exposure to cold appears to be a promising model for the induction of hypertension in rats without the need for surgical intervention, excessive doses of hormones, or genetic manipulation.** [P.S.E.B.M. 1990, Vol 195]

When rats are exposed chronically to air at 5°C, they increase their systemic blood pressure, the weight of the whole heart and left ventricle, and develop the syndrome of hypertension (1–6). These cold-exposed rats are also well known to increase their metabolic rate (7–9), circulating plasma levels of catecholamines (10), and metabolic responsiveness to norepinephrine and β-adrenergic agonists (11–14). Whether an increase in the concentration of norepinephrine in the plasma of cold-exposed rats plays a direct role in the development of hypertension is uncertain at present. Since the responsiveness of vascular smooth muscle from cold-treated rats administered graded doses of either norepinephrine or phenylephrine is reduced *in vitro* (13), as is the increase in blood pressure *in vivo* (4), it seems clear that the elevation of blood pressure in cold-treated rats cannot be associated with an increase in α-adrenergic responsiveness. Other

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mechanisms for the induction of hypertension must be sought.

Earlier studies from this laboratory showed that exposure of rats to 5°C for 3 to 4 weeks will result in elevation of blood pressure (1, 4, 15). Although the time course for development of hypertension after exposure to 5°C is now known, no studies have yet been carried out to determine whether there is a threshold ambient temperature above which hypertension does not occur when rats are exposed chronically to it. To assess this, the present study investigated the effect of two different ambient temperatures (5 ± 2 and 9 ± 2°C) on the time course for elevation of blood pressure in rats. In addition, the possibility that the weight of the rat at the time of exposure to cold might affect both the rate and magnitude of development of hypertension was studied. A final study assessed the strain specificity of cold-induced hypertension in rats.

Materials and Methods

Experiment 1: Effect of Two Different Ambient Temperatures on Development of Cold-Induced Hypertension in Rats. Forty male rats of the Blue Spruce Farms (Sprague-Dawley) strain weighing initially from 230 to 325 g were used. The animals were housed individually in hanging, stainless steel, mesh wire cages in temperature-controlled chambers at either 9 ± 2°C (n = 20) or 5 ± 2°C (n = 20). The chambers were identical and were illuminated from 7 AM to 7 PM daily. The rats were provided with Purina Laboratory Chow and tap water *ad libitum*. Body weight and blood pressure of all rats were measured weekly. The method used for measurement of systolic blood pressure was that described by Fregly (16), using a Narcobio Instruments Co. polygraph. All rats were removed from cold for 0.5 h prior to making this measurement. The weekly measurements of blood pressure were analyzed by a repeated measures, one-way analysis of variance (ANOVA). When a significant ($P < 0.05$) F value was obtained, Duncan's multiple range test was used to compare individual means.

Experiment 2: Effect of Body Weight on Development of Cold-Induced Hypertension in Rats. We have observed in our studies that older, heavier rats are less prone to develop hypertension as quickly as younger, less heavy rats. Since heavier rats usually have a greater content of body fat, a possibility existed that heavier rats might be better protected against, and therefore less stressed by, the effects of cold by virtue of the insulative qualities of their greater body fat content.

To accomplish our objective, data from five separate unpublished studies were used. In the first study (Experiment 7, 6 rats) the rats weighed initially 423 ± 7 g; in the second study (Experiment 8, 6 rats) the rats weighed 329 ± 8 g; in the third (Experiment 13, 20 rats) the weight was 320 ± 9 g; in the fourth (Experiment 15, 21 rats) the weight was 247 ± 5 g, while in the fifth (Experiment 17, 6 rats) the weight was 308 ± 8 g. These rats were placed in air at 5 ± 2°C and systolic blood pressures measured as described above at intervals for at least 42 days of cold exposure. All rats were males of the Blue Spruce Farms (Sprague-Dawley) strain. To assess the effect of body weight on the development of hypertension during exposure to cold, the mean time for systolic blood pressure to increase by 10 mm Hg above pre-cold exposure level was determined for each study.

Experiment 3: Effect of Exposure to Cold on the Development of Hypertension in Rats of the Fischer 344 Strain. Twelve male rats of the Fischer 344 strain were used. They were maintained under conditions identical to those described in Experiment 1. The rats weighed approximately 225 g at the time of exposure to cold. The rats were separated at random into two equal groups. After initial baseline measurements of body weight and systolic blood pressure, one group was exposed to cold (5 ± 2°C) while the second was kept at 26 ± 2°C. Blood pressures and body weights of the two groups were measured at intervals thereafter for 44 days.

Results

Experiment 1. Within 7 days of exposure to cold, the systolic blood pressure of the rats exposed to 5°C was elevated significantly ($P < 0.01$) above that of the group exposed to 9°C. Blood pressure reached a maximal level by 14 days of exposure to 5°C and remained significantly elevated for the remainder of the 40 days of exposure to 5°C (Fig. 1). In contrast, the rats that

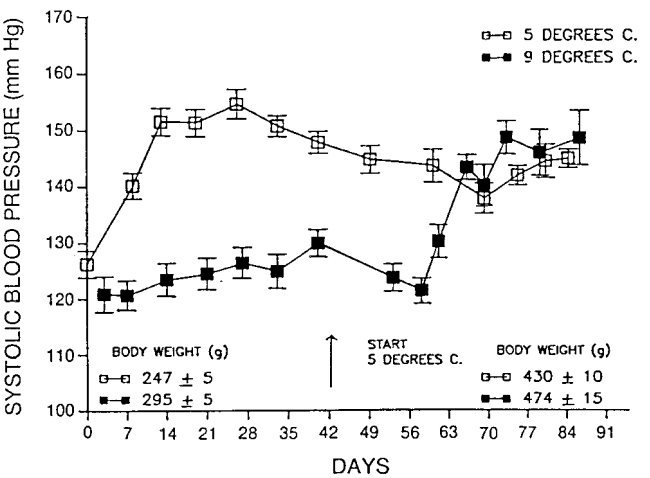

Figure 1. Systolic blood pressures of rats exposed to 5 and 9°C are shown at weekly intervals following initial exposure to these ambient temperatures. The groups are designated in the figure. At 42 days the temperature was reduced to 5°C for the rats that had been exposed to 9°C at the beginning of the experiment. Mean body weight of each group is shown at the beginning and end of the experiment. One standard error is set off at each mean.

were exposed to 9°C had no significant change in their systolic blood pressure during the 40 days of exposure. At this time, the temperature in their chamber was reduced to 5 ± 2°C. Twenty-five days later (67 days after initial exposure to cold), systolic blood pressure increased to a level significantly greater than that observed during prior exposure to 9°C. Systolic blood pressure remained significantly elevated for the remainder of the experiment.

As seen in Figure 1, the blood pressures of the group exposed to 9°C tended to increase by about 8 mm Hg over the 40 days of exposure to this temperature. Thus, it is possible that these animals would have developed a significant elevation of systolic blood pressure if allowed to remain at this temperature long enough.

Body weight (Fig. 1) of the group exposed to air at 5°C was significantly ($P < 0.01$) less than that of the group exposed to air at 9°C. However, the difference in body weight from the beginning of the experiment to the end remained relatively constant for the two groups.

Experiment 2. Systolic blood pressures of groups of rats whose body weights differed at the time of entrance into cold are shown in Figure 2. The rats in Experiment 7 (423 ± 7 g) were the heaviest and had the smallest rise in blood pressure (approximately 17 mm Hg). Rats of Experiments 8 and 13 were similar in body weight at the time of entrance into cold (329 ± 8 and 320 ± 9 g, respectively). The maximal levels of blood pressure attained were similar (approximately 150 mm Hg), although rats of Experiment 8 had a greater maximal change in blood pressure (37 mm Hg) compared with those in Experiment 13 (20 mm Hg). The rats weighing the least (Experiment 15, 247 ± 5 g) had a maximal increase in blood pressure to approximately 150 mm Hg and a change in blood pressure from the control period of 32 mm Hg. The days required to increase systolic blood pressure by 10 mm Hg above pre-cold exposure level are graphed against mean body weight at the time of entrance into cold for each group represented in Figure 3. There was a highly significant ($P < 0.01$) direct linear relationship ($r = 0.96$) between the two variables.

Experiment 3. The systolic blood pressures of rats of the Fischer 344 strain became elevated during exposure to cold (Fig. 4A). The first significant ($P < 0.01$) difference between the blood pressures of cold-treated and control rats occurred on the 16th day of exposure to cold. Maximal elevation of blood pressure occurred within 21 days. Body weights (Fig. 4B) of the two groups did not differ significantly throughout the period of exposure to cold, although there was a trend for the cold-exposed rats to gain weight more slowly than controls.

Discussion

The results of these studies suggest that there is a temperature threshold for the elevation of blood pressure in rats exposed chronically to cold. Thus, rats exposed to 9°C did not become hypertensive even after 40 days of exposure to cold. However, when the ambient temperature was reduced to 5°C, blood pressure became elevated within 25 days of continuous exposure. These results suggest that the temperature threshold for elevation of blood pressure in rats lies between 5 and 9°C.

Previous studies from this laboratory have shown that an elevation of blood pressure occurs within 3 to 4 weeks after exposure of rats to 5°C (1, 4). The rats

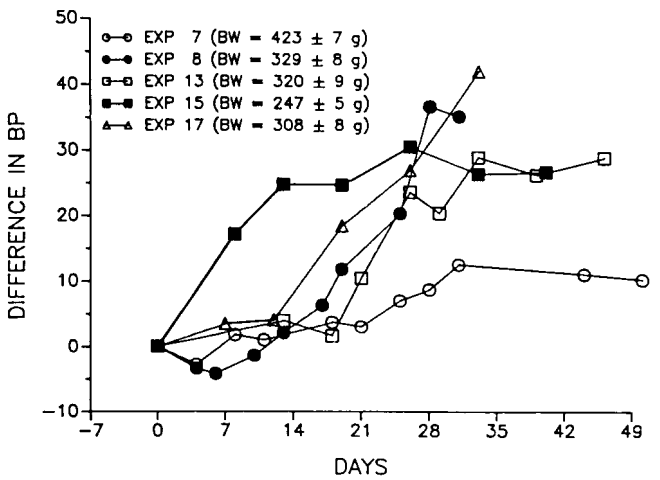

Figure 2. The mean difference in systolic blood pressure from pre-cold exposure value is shown at various times after exposure to cold (5°C) for rats from five separate experiments in which body weight varied at the time of entrance into cold. The designation for each experiment and the mean body weight of the group at the time of entrance into cold are shown in the upper left.

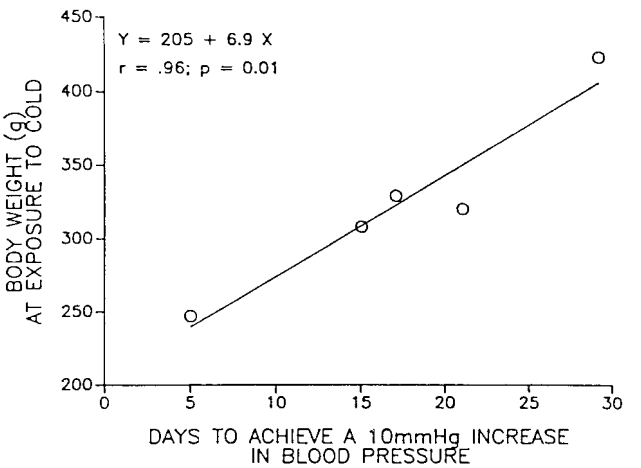

Figure 3. Relationship between body weight and the number of days of exposure to cold (5°C) that were required to achieve a 10 mm Hg increase in systolic blood pressure for the rats from the five separate experiments shown in Figure 2. The equation describing this relationship, as well as the correlation coefficient for the relationship, are shown.

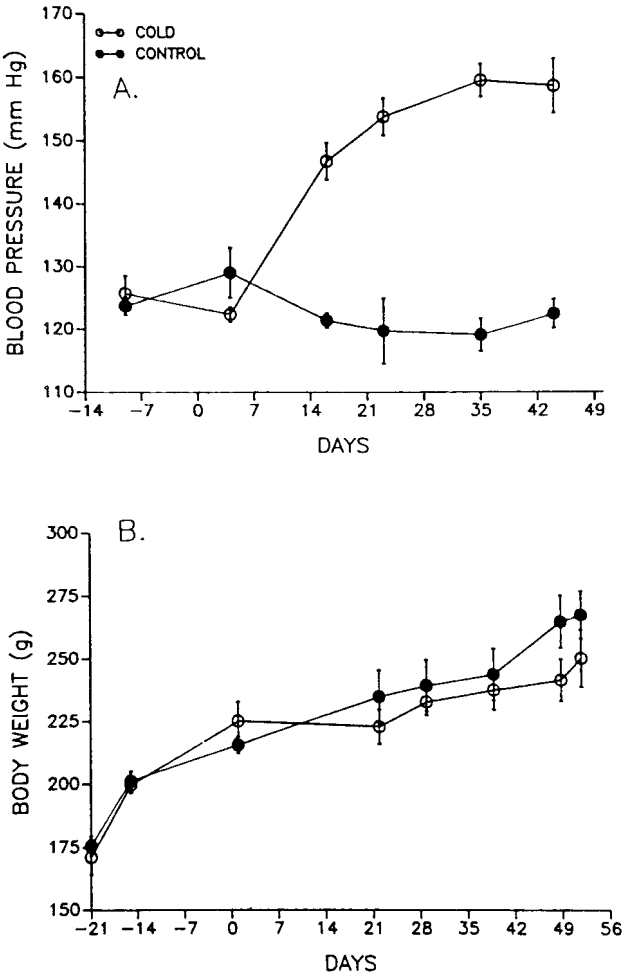

Figure 4. Systolic blood pressures of rats of the Fischer 344 strain exposed to cold and their controls maintained at 26°C are shown in A. The groups are designated in the figure. Cold exposure began at 0. One standard error is set off at each mean. Mean body weights of two groups of rats throughout the study are shown in B. One standard error is set off at each mean.

exposed to 5°C after exposure to 9°C had an elevation of blood pressure that occurred within this time frame. The rats initially exposed to 5°C had their first significant elevation of blood pressure somewhat sooner, i.e., within 7 days. Although this differs from the earlier observation of 3 weeks, it suggests that other uncontrolled variables influence the time course for development of the first significant elevation of blood pressure during exposure to cold.

It is now apparent that one such variable affecting the rate of elevation of blood pressure is the weight of the rat at the time of exposure to cold. The results of the second experiment suggest that there is a direct relationship between the time required to increase blood pressure by 10 mm Hg above pre-cold exposure level and weight of the rat at the time of entrance into cold (Fig. 3). The heavier rats required more time to increase their blood pressure by 10 mm Hg than less heavy rats. We suggest that the stress of exposure to cold may be less in heavier rats due to the insulative properties of the excess adipose tissue. This suggestion, however, will require testing.

The results of the third experiment indicate that rats of the Fischer 344 strain also became hypertensive when exposed chronically to cold. About 10 days were required to increase blood pressure 10 mm Hg above pre-cold exposure level. Since the rats were 225 g at the time of exposure to cold, the data for the Fischer strain fall below those of the Sprague-Dawley strain in Figure 3. This suggests that there may be a downward shift in the line of Figure 3 for this strain. This would be a reasonable expectation since rats of the Fischer strain are well known to grow at a slower rate than those of the Sprague-Dawley strain. The reduced rate of growth is an important factor in the use of the Fischer strain by researchers in the field of aging. In general, however, the results of the third experiment indicate that the development of an elevated blood pressure during exposure to cold is not specific to the Sprague-Dawley strain, but can occur in the Fischer 344 strain as well.

The results of this, and earlier studies (1–4), suggest that chronic exposure of rats to cold air can induce hypertension. This appears at present to be a unique paradigm in which hypertension occurs without either surgical intervention, administration of excessive doses of hormones and drugs, or genetic manipulation. Chronic exposure to cold is a promising model for induction of hypertension in rats.

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