Cardiovascular and metabolic responses of hypertensive and normotensive rats to one week of cold exposure

J. B. CHAMBERS, T. D. WILLIAMS, A. NAKAMURA, R. P. HENDERSON, J. M. OVERTON, AND M. E. RASHOTTE. Cardiovascular and metabolic responses of hypertensive and normotensive rats to one week of cold exposure. Am J Physiol Regulatory Integrative Comp Physiol 279: R1486–R1494, 2000.—Challenges to energy homeostasis, such as cold exposure, can have consequences for both metabolic and cardiovascular functioning. We hypothesized that 1-wk cold exposure (4°C) would produce concurrent increases in metabolic rate (V_{O_2}; indirect calorimetry), heart rate (HR), and mean arterial blood pressure (MAP) measured by telemetry. In the initial hours of change in ambient temperature (T_{a}), both spontaneously hypertensive rats (SHRs) and normotensive Sprague-Dawley rats showed rapid increases (in cold) or decreases (in rewarming) of V_{O_2}, HR, and MAP, although the initial changes in MAP and HR were more exaggerated in SHRs. Throughout cold exposure, HR, V_{O_2}, food intake, and locomotor activity remained elevated but MAP decreased in both strains, particularly in the SHR. During rewarming, all measures normalized quickly in both strains except MAP, which fell below baseline (hypotension) for the first few days. The results indicate that variations of T_{a} produce rapid changes in a suite of cardiovascular and behavioral responses that have many similarities in hypertensive and normotensive strains of rats. The findings are consistent with the general concept that the cardiovascular responses to cold exposure in rats are closely related to and perhaps a secondary consequence of the mechanisms responsible for increasing heat production. Hypertension; telemetry; ambient temperature; spontaneously hypertensive rat; Sprague-Dawley rat; energy balance; ingestive behavior; heart rate.

EXPOSURE TO COLD AMBIENT temperature (T_{a}) produces a strong homeostatic challenge to homeothermic vertebrates. In mammals, a primary response to cold is elevation of metabolic heat production via nonshivering thermogenesis (15). This response is mediated by increased efferent sympathetic nervous system activity (27) and is very rapid; significant increases in uncoupling protein-1 mRNA in brown adipose tissue (BAT) occur in lean rats within 2.5 h of cold exposure (4). The pattern of augmented sympathetic nervous system activity in the cold has been studied by tissue noradrenaline interrelationships between the cardiovascular and metabolic responses of spontaneously hypertensive rats (SHRs) and normotensive Sprague-Dawley (SD) rats when they are exposed to 4°C cold for 1 wk and when they return to the baseline T_{a} (23°C). The experimental situation we employed (36) offers the advantage of simultaneous, unobtrusive measurement of relevant variables during the entire daily cycle; HR and MAP were measured through telemetry and metabolic rate was measured by indirect calorimetry (V_{O_2}). Behavioral responses (food and water intake, locomotor activity) also were measured. We hypothesized that there would be a coordinated increase in HR, MAP, and V_{O_2} in each strain, but possibly heightened responsivity in the SHR strain, which has been shown to respond to some environmental stimuli with exaggerated cardiovascular and sympathetic responses (16, 20, 21).

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RESEARCH METHODS

Animals and housing. Eight male SHRs and seven normotensive SD rats (both from Harlan Sprague Dawley, Indianapolis, IN) were 12 ± 1 wk of age at the beginning of the experiment and had been housed for similar periods of time in standard laboratory conditions where Ta equals ~21–22°C. The rats were anesthetized (pentobarbital sodium, 50 mg/kg) and instrumented with a catheter in the descending aorta coupled with a sensor and transmitter (TA11PA-C40; Data Sciences, St. Paul, MN) for telemetric monitoring of cardiovascular status. During recovery from surgery, the rats were housed individually in cages similar to the experimental cages, with a 12:12 h-light-dark cycle and Ta 23°C. Each experimental cage (49 by 22 by 17 cm) had a polycarbonate base with an 8-cm lip containing animal bedding and sides and top constructed of wire mesh so that adequate air mixing could be achieved for the purpose of indirect calorimetry (see below). Powdered chow (Purina 5001; physiological fuel value, 3.3 kcal/g) in a food jar was reached by entering a modified stainless steel tunnel feeder that minimized spillage. Water was obtained by licking a tube located nearby. Each experimental cage was housed in a separate metabolic chamber that provided precise control of Ta (~±0.1°C). The daily light-dark schedule (12:12 h) was imposed by lighting an overhead incandescent lamp (illumination ~60 lux of 2,250°K light) for 12 h each day, beginning at 2200 local time; the chamber was completely dark for the remaining 12 h. Rats remained in the metabolic chambers continuously except for a brief (~15 min) daily maintenance period ~2 h before lights off.

Indirect calorimetry. The apparatus and procedures used for determination of metabolic rate have been described previously (26). Briefly, each experimental cage housed an individual rat placed in an acrylic metabolic chamber (40-liter capacity) where oxygen consumption (VO2) and carbon dioxide production (VCO2) were measured every 2.5 min by open circuit respirometry (2 l/min) using a modification of the approach described by Bartholomew et al. (3) to isolate successive samples. VO2 was adjusted for mass (ml·min⁻¹·kg⁻⁰·⁷⁵) (5). A separate value for respiratory quotient (RQ; VCO2/VO2) was calculated for the entire 12-h dark phase and for the first 10 h of the light phase.

Cardiovascular telemetry. A telemetry receiver (RPC-1; Data Sciences) was positioned under the rat cage within the metabolic chamber. The pulses from the receiver were relayed to a calibrated pressure output adapter (R11CPA; Data Sciences), where they were converted to analog voltages representing blood pressure waveforms. The signals were amplified, filtered with a time constant of 1 ms, and relayed to a 12-bit analog-to-digital converter board in a computer that sampled the signals at 500 Hz with a resolution of 0.1 mmHg. Custom-written online software processed the blood pressure waveform, detected the systolic and diastolic blood pressures, and calculated MAP and HR. The average systolic and diastolic blood pressures, MAP, and HR were calculated for each 30-s period of the light-dark cycle and were stored on a floppy disk as 16-bit integers for off-line analysis. Extremely low or high blood pressures resulting from transient signal interference occurred rarely and were automatically detected and excluded from the 30-s averages.

Food and water intake. Daily food and water intakes were obtained by measuring on/off weights of the feeder (corrected for spillage) and water bottle during the daily maintenance period. The feeder and water bottle assemblies were equipped with a photobeam arrangement that indicated when the rats were ingesting food or water (see Ref. 36 for details).

Locomotor activity. One-half of the rats were run in metabolic chambers instrumented to record locomotor activity. These chambers rested on a fulcrum positioned across the narrow axis of the cage in which the rat lived. One end of the chamber was attached to a stiff strain gauge transducer (alpha-load beam; BLH electronics) that prevented rocking of the chamber on the fulcrum and allowed determination of the position of the rat within the chamber along the long axis. The electronic signal from the strain gauge was amplified, low-pass filtered with a 3-dB point of 10 Hz, and routed to an analog-to-digital converter where it was sampled at 20 Hz, thus allowing determination of the position of the animal’s center of gravity along the long axis. To detect locomotor activity as the animal moved in the chamber, the rate of change in the chamber’s center of gravity was low-pass filtered with an average time of 500 ms. Locomotor activity, measured in meters traveled, was accumulated in 30-s periods and stored with a 1-mm resolution.

Protocol. After recovery from surgery and the initial adaptation to the housing conditions, rats were transferred to the metabolic chambers. To avoid a learning effect, day 2 of the 5-day cold exposure period was used for one-half of the rats to be returned to 23°C at the onset of the dark phase. The cardiovascular, metabolic, ingestive behavior, locomotor-activity, and body weight responses to cold exposure were observed for 1 wk. Each rat was removed from the cold for only 5–10 min/day during the daily maintenance period when the food, water, and rat were weighed, and the food, water, and chamber-bedding were refreshed. After the 7-day exposure to 4°C, Ta was returned to 23°C at the onset of the dark phase at a rate of 10°C/h, beginning at the onset of the dark phase. Because of a computer malfunction, SD rats remained in cold for 1 additional day.

Data analysis and statistics. Cardiovascular and locomotor measures were collected and stored in 30-s bins; metabolic measures were collected and stored in 2.5-min bins. All measures were transformed into 10-min bins that were used in computing separate values for the light and dark phases. Because the final 2 h of the light phase (which began with daily chamber maintenance) were excluded in these computations, values reported for dark and light phases are based on 12 and 10 h of data, respectively. The responses of the two strains were compared by repeated-measures ANOVA. Two main sets of analyses were carried out. “Cold” analyses were concerned with changes in body mass, food and water intake, MAP, HR, VO2, RQ, and locomotor activity during 7 days of cold exposure (data for the eighth day of cold experienced by the SD rats are plotted in the figures but are not included in the statistical analyses comparing strains. The responses of SD rats on this extra day of cold were similar to day 7 in each measure.) “Recovery” analyses were concerned with the extent to which the measured variables recovered to baseline levels during the 5 days when Ta was 23°C after cold exposure ended. In both the cold and recovery analyses, the baseline level for each measure was represented by the mean of the 3 baseline days immediately preceding cold exposure. In measures where separate dark- and light-phase data were obtained, separate ANOVAs were carried out for each phase. Comparable analyses were also carried out on “basal data” calculated for the MAP, HR, and VO2 measures. Basal data were obtained by sorting light- and dark-phase data each day to identify the twelve 10-min bins with the lowest VO2 values in each phase. Cumulatively, these data identified 2 h in each phase when metabolic rate was lowest. Mean values of MAP,
HR, and \( \dot{V}O_2 \) calculated for each rat during these basal periods were used in the basal analyses. Tukey tests determined significant differences between means in post hoc pairwise comparisons. Statistical significance levels were set at \( P < 0.05 \). In all analyses, \( n = 8 \) for SHRs and \( n = 7 \) for SD rats, except for the following measures where \( n = 4; \) 1) locomotor activity (only 4 chambers were instrumented to quantify locomotor data), 2) SHR caloric intake (data from 4 SHRs implementing an improved feeder design that minimized food spillage were utilized), and 3) SHR RQ (due to temporary measurement difficulty, \( \dot{V}CO_2 \) data for 4 SHRs were unreliable during cold exposure).

**RESULTS**

*Body weight, caloric intake, and water intake.* Figure 1A indicates that on baseline and during exposure to cold, SD rats weighed about 65 g more on average than SHRs (\( F_{\text{Strain}} = 17.04, \text{df} = 1.13, P = 0.001 \)), and there was some indication of weight loss (about 6 g on average) in response to cold (\( F_{\text{Days}} = 3.47, \text{df} = 7.91; P < 0.01 \)). In the recovery period, both strains increased body weight (\( F_{\text{Day}} = 25.32, \text{df} = 5.65; P < 0.001 \)), averaging about 4% above baseline level by the last day (Fig. 1A). Daily food intake (Fig. 1B), which did not differ between the strains in any part of the experiment, promptly increased in response to cold exposure (\( F_{\text{Days}} = 24.22, \text{df} = 7.63; P < 0.001 \)) and returned to baseline levels 1 day after \( T_a \) returned to 23°C (\( F_{\text{Days}} = 4.13, \text{df} = 5.65; P < 0.01 \); post hoc tests). During cold, food intake reached a plateau about 50% higher than baseline by about the fifth day. SD rats drank about 9 ml more water each day than SHRs (Fig. 1C), but this strain difference reached significance only in the recovery period (\( F_{\text{Strain}} = 8.10, \text{df} = 1.13, P < 0.05 \)). Cold exposure resulted in an increase in water intake in both strains (\( F_{\text{Days}} = 14.89, \text{df} = 7.90; P < 0.001 \)), but this increase was sluggish relative to the rapid change found in food intake; post hoc tests indicated that water intake first became reliably greater than baseline on day 3 of cold. Water intake leveled off ~25–30% above baseline by about the fifth day of cold exposure. In the recovery period, water intake decreased to baseline by the third day (\( F_{\text{Days}} = 9.26, \text{df} = 5.64; P < 0.001 \); post hoc tests).

The main findings with respect to cardiovascular and energetic responses are summarized in Figs. 2–4. Analyses of the full-phase data in Fig. 2 identified the key effects and are reported in detail. Parallel analyses carried out on the basal data shown in Fig. 2 yielded mostly similar results, but occasional exceptions are of interest and are noted.

**MAP.** MAP was higher in SHRs than in SD rats in both the cold and recovery analyses of light- and dark-phase data (\( F_{\text{Strain}} = 35.26, \text{df} = 1.13, P < 0.001 \); Fig. 2A). Exposure to cold resulted in elevated MAP in both strains in the light and dark phases (\( F_{\text{Days}} = 74.53, \text{df} = 7.91; P < 0.001 \)) but not in an equivalent fashion (\( F_{\text{Strain} \times \text{Day}} = 13.51, \text{df} = 7.91; P < 0.001 \)); pairwise comparisons indicated that cold initially induced a greater elevation above baseline in SHRs. This effect is shown most clearly in Fig. 3, A and B. By the fourth (light phase) or fifth (dark phase) day in cold, the greater elevation in MAP shown by SHRs disappeared; in the remainder of the cold exposure, the strains remained nondifferential (dark phase) or actually reversed such that SHRs had a smaller elevation above baseline than SD rats (light phase). On days 5 and 6 of cold, light-phase MAP was statistically indistinguishable from baseline in SHRs but remained statistically above baseline on all cold days in SD rats (Fig. 3B); in the dark phase, however, MAP in cold remained significantly elevated above baseline in both strains (Fig. 3A).

The analysis of basal MAP data (Fig. 2B) highlighted the strain differences noted in which MAP recovered to baseline during cold exposure in SHRs but not in SD rats. In this measure, pairwise comparisons for SHRs indicated that light-phase basal MAP did not differ significantly from baseline on days 5–7 of cold and that dark-phase basal MAP did not differ significantly from baseline on days 5 and 6 of cold. This dark phase result, which was not found in the analysis of full-phase data,
may reflect a greater influence of locomotor activity (see Fig. 5) in full-phase data than in basal data where locomotion is unlikely to be a factor.

The full-phase data in Fig. 2A show that when $T_a$ returned to 23°C in the recovery period, MAP immediately decreased in the light and dark phases and continued to change across days ($F_{Days} \geq 23.90$, df = 5,65; $P < 0.001$). Strain differences were found in the recovery ($F_{Strain \times Day} \geq 3.36$, df = 5,65; $P < 0.01$), which are most clearly summarized in Fig. 3, A and B. Pairwise comparisons indicated that the initial response to the rewarming of $T_a$ was greater in SHRs, which showed a relatively large decrease in MAP below baseline level. Subsequently, baseline values were recovered more rapidly in SD rats than in SHRs (Fig. 3, A and B); dark-phase MAP recovered to baseline by day 4 of the recovery period in SD rats but did not fully recover in SHRs; light-phase MAP recovered to baseline by day 5 in SHRs.

Figure 4, A and B, highlights the rapidity with which MAP responded when $T_a$ decreased at the beginning of cold exposure and increased at the beginning of the recovery period. During the 4-h period after $T_a$ began to decrease or increase, MAP changed significantly ($F_{Bin} \geq 6.80$, df = 23,299; $P < 0.001$). Furthermore, it is shown that SHRs were more responsive to the changes than were SD rats in these periods (cold onset: $F_{Strain} = 67.22$, df = 1,13; $P < 0.001$; $F_{Strain \times Bin} NS$; cold offset: $F_{Strain} NS$; $F_{Strain \times Bin} = 2.82$, df = 23,299; $P < 0.001$).

HR. In analyses of both cold and recovery data in the light and dark phases, HR was significantly lower in SHRs than in SD rats ($F_{strain} \geq 20.72$, df = 1,13; $P < 0.001$), which reflected the baseline difference as well (Fig. 2C). HR became elevated in both phases on exposure to cold ($F_{Days} \geq 112.72$, df = 7,91; $P < 0.001$), and in the light phase, the strains showed comparable changes during cold exposure (no strain-
by-day interaction); after an initial increase of about 
160 beats/min above baseline values, HR decreased to
about 120 beats/min above baseline values by the final
3 days in cold (Fig. 3D). In the dark phase, however, a
significant interaction occurred ($F_{\text{Strain} \times \text{Day}} = 3.29,$
$df = 7.91; P < 0.01$) and post hoc tests indicated that
the rate of increase in HR across the first 3 days in cold
was greater in the SHRs (Figs. 2C and 3C). During the
recovery period, the changes in HR in both the light
and dark phases ($F_{\text{Days}} = 21.52, df = 5.65; P < 0.001$)
showed no significant strain-by-day interactions. Post
hoc tests indicated that after the first day of recovery,
when HR was still above baseline, there was a gradual
decrease to below baseline values that became statis-
tically significant in the dark phase by day 4 and in the
light phase by day 3.

Figure 4, C and D, shows that large and rapid
changes in HR occurred during the 4-h period after $T_a$

began to decrease or increase ($F_{\text{Bin}} = 8.13, df = 23.299,$
$P < 0.001$). Although on average SHRs became more
responsive to cold onset and offset during these peri-
ods, a between-strain difference was found only in cold
offset ($F_{\text{Strain} \times \text{Bin}} = 3.09, df = 23.299; P < 0.001$).

$\dot{V}O_2$. There was no significant main effect of strain in
analyses of cold or recovery $\dot{V}O_2$ data (Figs. 2, E and F,
and 3, E and F). Exposure to cold resulted in a large
increase in $\dot{V}O_2$ in both phases ($F_{\text{Days}} = 285.74, df = 7.91; P < 0.001$) that differed between strains only in
the dark phase ($F_{\text{Strain} \times \text{Day}} = 2.86, df = 7.91; P =
0.01$). Pairwise comparisons indicated that dark-phase
$\dot{V}O_2$ was significantly greater in SD rats on days 3 and
6 of cold ($P < 0.05$; Figs. 2E and 3E). In the recovery
analyses, the only significant effect was a change
across days in both phases ($F_{\text{Days}} = 5.20, df = 5.65,$
$P < 0.05$), which pairwise comparisons indicated was
attributable to above-baseline $\dot{V}O_2$ on the first day,
followed by the recovery to baseline on subsequent days in the recovery period.

Figure 4, E and F, shows that \( \dot{V}O_2 \) changed rapidly during the 4-h period after \( T_a \) began to decrease or increase \((F_{Bin} = 4.70, df = 23,299; P < 0.001)\). No statistically significant difference associated with strain was found in these analyses.

**RQ.** Analysis of the RQ data in the dark and light phases indicated some differences between the strains. In the baseline period, dark-phase RQ was significantly higher in SHRs than in SD rats \((0.98 \pm 0.005 \text{ vs. } 0.94 \pm 0.005, \text{ respectively})\); the light-phase values for the two strains did not differ \((\text{SHRs, } 0.95 \pm 0.005; \text{ SD rats, } 0.92 \pm 0.005)\). The principal effect of the cold exposure was a decrease in RQ that averaged about 0.06 in the dark phase and 0.045 in the light phase on the early days in cold. On the later days in cold, there was some recovery in RQ and it promptly returned to baseline when \( T_a \) increased in the recovery period.

**Locomotor activity.** Figure 5 shows that exposure to cold resulted in an increase in locomotor activity by the two strains in both the dark and the light phases.
were obtained by the telemetry method. Furthermore, the possibility of reduced blood volume is indirectly supported by the delayed increase in fluid consumption that occurred 3 days after initiation of cold exposure. However, SD rats also showed a delayed increase in fluid intake, although MAP remained significantly elevated compared with precold baseline levels for 23 days after cold exposure ends. However, these data on the kinetics of change in MAP are limited by infrequent measurements; after the initial 24-h postcold period, MAP was measured at only three time points over 3 wk. The more complete picture provided by our data shows that after 1 wk in 4°C, an increase in $T_a$ to 23°C is accompanied by 1) a decrease in MAP that is evident even during the first few hours after $T_a$ change begins, 2) a period of postcold hypotension for several days, which is more severe in SHRs than in SD rats, and 3) the development of bradycardia between 3 and 4 days after removal from cold. Additional studies of the kinetics of changes in cardiovascular functioning during long-term cold exposure and during postcold recovery periods would provide important information about the mechanisms responsible for cold-induced changes in hypertension. Such studies would be best carried out using telemetry measurement of cardiovascular responses.

**DISCUSSION**

The present experiment shows that MAP, HR, and $V_O^2$ are promptly elevated by cold onset and decreased by cold offset in hypertensive and normotensive rats. With two main exceptions, the pattern of results found in the two strains was similar. One difference was that in the MAP and HR measures, the initial response by SHRs to change in $T_a$ was relatively large compared with the normotensive SD rats. At cold onset, the SHRs had greater elevations in these measures and at cold offset the SHRs had greater depression in MAP, which actually fell significantly below baseline levels for several days in both strains, indicating a postcold period of hypotension. The other difference was that during several days of cold exposure, the SHRs showed a greater tendency to normalize MAP, especially in the light phase when locomotor activity and feeding were less likely to occur. In fact, after several days of cold exposure, basal levels of MAP decreased to values that were statistically indistinguishable from baseline in the SHRs. Although MAP in SD rats also decreased over time during cold exposure, it remained significantly elevated above baseline throughout the cold period. The overall pattern of our results is consistent with the hypothesis that the initial metabolic and cardiovascular responses to cold exposure reflect elevated sympathetic activity that is required to defend core body temperature. It is suggested that as sympathetic activation is sustained in cold, compensatory mechanisms become engaged that help normalize MAP, and these mechanisms are expressed more fully in SHRs than in SD rats. When cold is abruptly terminated after 1 wk, these compensatory mechanisms are expressed as hypotension for a few days.

Fregly and colleagues (11, 12, 23, 24, 29, 31–33) have established that cold exposure elevates MAP through both neural and renal mechanisms. The reported time course of activation of these mechanisms likely depends on the measurement technique for MAP. Many of Fregly's experiments employed the tail-cuff method for measuring MAP and that work indicated rather sluggish changes in MAP in response to cold (e.g., several days or weeks). However, one study from his laboratory reported a rapid response to cold onset when MAP was measured (in SD rats) by the chronic catheterization method (12). That finding is more in line with our present results that were obtained by the telemetry method. Furthermore, our telemetry data and Fregly's data from the catheterization method (12) also indicate that an increase in $T_a$ following cold exposure inhibits the signals that elevate HR and $V_O^2$ during cold. This is perhaps mediated by withdrawal of sympathetic activation following cold offset. Fregly's data showed that a decrease in MAP occurred within hours of rewarming, but that MAP rebounded over a period of several days and then remained elevated compared with precold levels even 23 days after cold exposure ends. However, these data on the kinetics of change in MAP are limited by infrequent measurements; after the initial 24-h postcold period, MAP was measured at only three time points over 3 wk. The more complete picture provided by our data shows that after 1 wk in 4°C, an increase in $T_a$ to 23°C is accompanied by 1) a decrease in MAP that is evident even during the first few hours after $T_a$ change begins, 2) a period of postcold hypotension for several days, which is more severe in SHRs than in SD rats, and 3) the development of bradycardia between 3 and 4 days after removal from cold. Additional studies of the kinetics of changes in cardiovascular functioning during long-term cold exposure and during postcold recovery periods would provide important information about the mechanisms responsible for cold-induced changes in hypertension. Such studies would be best carried out using telemetry measurement of cardiovascular responses.

**What mechanisms might account for the compensatory decrease in MAP toward baseline during sustained cold exposure in SHRs?** Because we did not measure cardiac output in these studies, we do not know the respective contributions of cardiac output and systemic vascular resistance to the arterial blood pressure response during sustained cold and rewarming. It has been shown previously that cardiac output increases during cold exposure (1, 13, 35). Atterhog et al. (1) found increased MAP and cardiac output and lowered systemic vascular resistance in humans. Hales et al. (13) also reported increased cardiac output, as well as lowered total peripheral resistance (TPR) in cold sheep, although the reduction in TPR was not statistically significant. Although we did not measure cardiac output or TPR, the sustained significant increases in HR and $V_O^2$ throughout cold exposure suggest that cardiac output remains elevated during cold exposure. However, compensatory reductions in MAP during sustained cold may be due to either reductions in stroke volume (see below) or systemic vascular resistance.

A possible explanation of reduction in MAP during sustained cold is pressure-mediated natriuresis and diuresis, leading to a reduction in circulating blood volume. Cold exposure is known to produce diuresis (11). The possibility of reduced blood volume is indirectly supported by the delayed increase in fluid consumption that occurred 3 days after initiation of cold exposure. However, SD rats also showed a delayed increase in fluid intake, although MAP remained significantly elevated compared with the precold baseline. The postcold hypotension that we observed within hours of beginning the rewarming in $T_a$ may also...
indirectly support a role for reduced blood volume during cold exposure. Two recent reports have indicated that blood volume is actually increased by 1 wk of cold exposure (28, 33). However, in one of these reports, it is clear that animals were rewarmed during surgical implantation of catheters and measurement of blood volume (28). We did not measure the blood volume response to cold exposure.

The greater decrease in MAP shown by the SHR strain during cold exposure might be related to that strain’s exaggerated sympathetic reactivity (16, 20). The SHRs responded more strongly in the MAP measure than did SD rats when cold exposure began, and SHRs have been shown to have a greater plasma catecholamine response to acute cold stress (25). Thus it could be argued that the fall in MAP during the week of cold exposure simply reflects a gradual dissipation of the exaggerated sympathetic response to cold. However, this explanation is tempered by the fact that the HR response peaked on the third day of cold exposure in SHRs, whereas MAP began declining toward baseline after the first 24 h in cold. It is also possible that chronic sympathoexcitation during cold resulted in a reduced vasoconstrictor responsiveness, causing a decrease in vascular resistance and MAP. If this were the case, then the mechanisms involved would have to operate within just a few days to explain both the decrease of MAP in SHRs during cold and the recovery of MAP during the postcold period. The possibility should also be noted that changes in parasympathetic activity unrelated to sympathetic activity could mediate some of the observed strain differences in the MAP response to cold.

Ta has sometimes been reported to have different effects on metabolic rate (VO2) in SHRs and normotensive Wistar-Kyoto controls. Strain differences were reported in adult rats when Ta was in the range 25–32°C (38) and in infant rats when the Ta range was 17–23°C (18). However, others have reported no differences in VO2 between these strains in cold (5°C) or warm (35°C) conditions (37). Furthermore, an acute (90-min) exposure to cold (6°C) was found to result in no strain difference in either HR or lumbar sympathetic nerve activity (34). Thus whether differential sympathoexcitation between SHRs and SD rats during cold exposure can explain the MAP response in SHRs appears to be an unresolved issue. Our findings in the SD strain, similar to previous results by Fregly and Schechtman (12), show that MAP in the SD strain did not return to baseline levels.

Although it seems clear that the activation of the sympathetic nervous system is a major component of the cardiovascular responses during 1 wk of cold exposure (7, 23, 40), other mechanisms contribute to the cardiovascular outcomes of this homeostatic challenge. For example, intravenous administration of a neuropeptide Y receptor antagonist transiently lowers MAP in the cold-exposed borderlne-hypertensive rat (14). Thus peripheral neuropeptide Y release from sympathetic nerve terminals may contribute to cold-induced increases in blood pressure. An additional ramification of chronic elevation of effenter sympathetic nerve activity may be activation of the renin-angiotensin-aldosterone system. One week of cold exposure produced a severalfold increase in plasma ANG II levels (7). Interestingly, the increases in plasma ANG II and norepinephrine caused by cold exposure were prevented by pair feeding. We speculate that pair-fed animals were placed in severe negative energy balance and that the normal cold-induced elevation of sympathetic activity was prevented by the activation of homeostatic mechanisms due to diminished energy reserves.

In animals allowed to increase food intake during cold exposure, angiotensin-converting enzyme inhibition, angiotensin receptor blockade, and aldosterone receptor blockade have been shown to reduce MAP (see Ref. 31 for review). Thus there is substantial evidence for a role of the peripheral renin-angiotensin-aldosterone system in cold-induced hypertension. Furthermore, central angiotensin mechanisms also may be involved in cold-induced hypertension. Central administration of antisense oligonucleotides to both angiotensinogen mRNA and the AT1 receptor mRNA were shown to reduce MAP in animals with chronic (5 wk) cold-induced hypertension (24). Additional work is needed to elucidate how these mechanisms interact to alter MAP during acute and chronic exposure to cold.

There is a heterogeneous pattern of sympathoexcitation during cold exposure (9, 10, 17, 19, 22, 39). The evidence indicates that sympathetic activity is increased to both BAT and the heart but not the kidneys or the liver. Effector mechanisms for temperature regulation, including sympathetic outflow to BAT, are under control of the preoptic hypothalamus (6, 30). In addition to the preoptic area, multiple hypothalamic nuclei, including the paraventricular and ventromedial nuclei, appear to comprise an organized central network innervating BAT (2). Coronal transection caudal to the preoptic area strongly activates nonshivering thermogenesis (8), and thus pathways that emerge from the preoptic hypothalamus must chronically inhibit sympathetic activity to BAT. At least one target for these projections may be the rostral raphe pallidus. Disinhibition of GABAergic activity in this region by microinjection of bicuculline strongly increases sympathetic activity to BAT (22). Furthermore, acute exposure to cold (4°C for 4 h) increases fos expression in rostral raphe pallidus (22). It is tempting to speculate that this pathway could provide a mechanism for the concurrent increases in HR and nonshivering thermogenesis observed during cold exposure and rewarmin.

In summary, the overall pattern of our results indicates that variations of Ta produce rapid changes in a suite of cardiovascular and behavioral responses that have many similarities in hypertensive and normotensive strains of rats. The findings are consistent with the general concept that the cardiovascular responses to cold exposure in rats are closely related to, and perhaps a secondary consequence of, the mechanisms responsible for increasing heat production.
REFERENCES


