Dynamics of Brown Fat Thermogenesis in Week-Old Rats: Evidence of Relative Stability during Moderate Cold Exposure

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ABSTRACT

Neonates of many mammalian species, including humans, depend primarily on thermogenesis by brown adipose tissue as a defense against cold challenge. Although the steady-state thermogenic responses of brown adipose tissue to various air temperatures are well known, the dynamic responses have received relatively little attention. In this article, we examine the relative stability of brown adipose tissue thermogenesis during brief perturbations of air temperature. Specifically, week-old rats were allowed to settle at one of two levels of cold exposure. These two levels were defined on the basis of previous work as being moderate (30.5°C) or extreme (23°C). After pups had settled at these temperatures, they were exposed to positive or negative air temperature perturbations of approximately 3.7°C. Pups experiencing perturbations from the moderate air temperature, unlike those exposed to the extreme air temperature, exhibited organized thermogenic responses that allowed them to return quickly to their preperturbation conditions. These data suggest that brown adipose tissue thermogenesis is more stably controlled than has previously been suspected.

Introduction

In many newborn mammals, including humans, brown adipose tissue (BAT) is the primary heat-producing organ that forms part of a relatively simple but important system. During cold exposure, sympathetic activation of BAT warms blood that is then directed toward the heart, lungs, and cervical spinal cord, thus providing much-needed heat to critical organs during even modest thermal challenge (Smith 1964; Hull and Siegel 1965). In newborn rats, BAT's primary importance for autonomic thermoregulation is highlighted by the fact that these animals are hairless, show little vasomotor control, and cannot shiver until after they are 10 d old (Taylor 1960; Spiers and Adair 1986).

Over the past 30 years, much has been learned about the neurological, pharmacological, and biochemical characteristics of BAT functioning in the neonate (for reviews, see Girardier and Seydoux [1986]; Nedergaard et al. [1986]). Moreover, BAT thermogenesis in neonates has been studied in detail in a number of mammalian species, including guinea pigs (Brück and Wünnenberg 1970), rabbits (Hull and Segall 1965), and rats (Conklin and Heggeness 1971; Spiers and Adair 1986). Studies such as these have provided us with valuable information regarding the thermogenic responses of newborns, although there has been a relative emphasis on steady-state responses. For example, Spiers and Adair (1986) analyzed data after rat pups had been allowed at least 1 h to settle at a given air temperature (T_a). Although analyses of steady-state response are essential for determinations of thermoregulatory ability, the dynamic features of BAT thermogenesis can also inform our understanding of this system, as we illustrate in the present study.

Because BAT is located primarily in the interscapular region overlying the cervical spinal cord (Smith 1964), we can estimate the tissue's temperature with a thermocouple glued to the skin surface in the interscapular region (Spiers and Adair 1986; Blumberg and Alberts 1990). We can also estimate changes in BAT heat production by measuring oxygen consumption (Heim and Hull 1966). Then we can illustrate the dynamics of heat production in neonates by constructing a state space plot of oxygen consumption versus interscapular temperature (Blumberg and Stolba 1996). Figure 1 presents the state space plots for two individual week-old pups, one cooled from a T_a of 35.5°C to 30.5°C (designated a moderate challenge) and the other cooled to 23°C (designated an extreme challenge). Points A_1 and A_2 indicate the beginning of the experiment, when T_a is 35.5°C—for both pups, interscapular temperature is high and oxygen consumption is low, which indicates little or no BAT heat production. Next, T_a is decreased, and the pup experiencing a moderate challenge exhibits first a decrease in interscapular temperature and then a vertical trajectory to point B_1, as heat production (and thus oxygen consumption) increases and interscapular temperature remains constant. Similarly, the pup experiencing an extreme challenge also exhibits a vertical trajectory through the state space, but once maximal heat production is attained, interscapular temperature decreases to a lower value (B_2).

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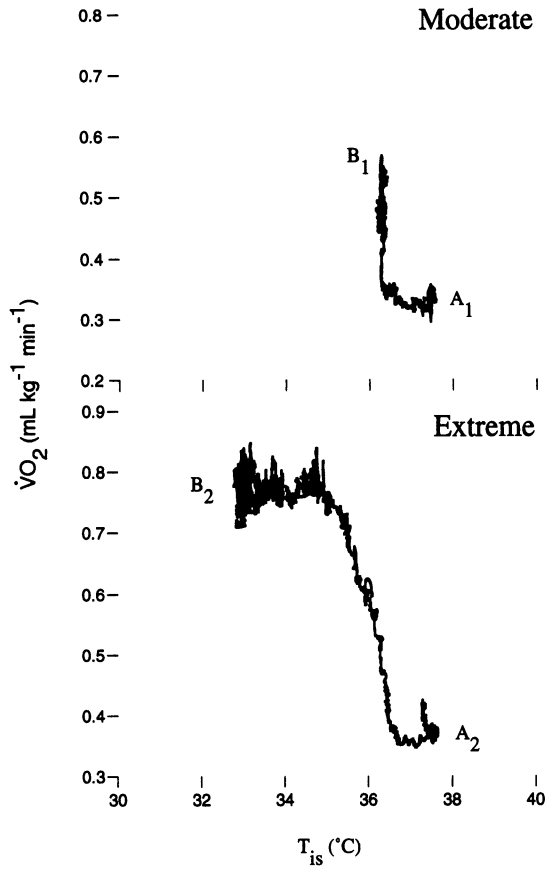

Figure 1. State space plots depicting oxygen consumption ($\dot{V}O_2$) versus interscapular temperature (T_{is}) for two representative week-old rats. At the beginning of the test, pups were maintained at a T_a of 35.5°C, indicated on the state spaces as points A_1 and A_2. After this initial period, T_a was decreased to either 30.5°C (*Moderate*) or 23°C (*Extreme*). Moderate cold exposure elicited a trajectory from A_1 to B_1 (elapsed time = 65 min), whereas extreme cold exposure elicited a trajectory from A_2 to B_2 (elapsed time = 105 min).

Given these two distinct responses to cold challenge, the following question was asked: Are points B_1 and B_2 equivalent in that they represent the arbitrary settling points of the system, or can the two settling points be distinguished on the basis of their relative stability? Dynamic systems theory, which is increasingly being applied to physiological problems (Garfinkel 1983), provides a framework in which to evaluate the relative stability of settling points (Thelen and Smith 1994; Kelso 1995). Specifically, when a stable settling point has been established, it should be relatively impervious to environmental perturbation—the settling point should be reestablished quickly. In contrast, when an unstable settling point has been established, it should be relatively sensitive to environmental perturbation—the settling point should be reestablished slowly or not at all. Thus, by definition, if B_2 is less stable than B_1, then a pup experiencing an extreme challenge should not return to B_2 after a brief perturbation of T_a, or if it does return, it should do so more slowly.

In the present experiment, we assessed the relative stability of BAT thermogenesis during T_a perturbation. Two conditions were used. Under the first condition, pups were allowed to settle at a moderate T_a (30.5°C) and were then exposed to a brief 3.7°C increase (n = 4) or decrease (n = 4) in T_a. Under the second condition, pups were allowed to settle at an extreme T_a (23°C) and were then exposed to an identical increase (n = 4) or decrease (n = 4) in T_a. The effects of these perturbations on pups' physiological responses were monitored continuously.

Material and Methods

Subjects

Sixteen 7-8-d-old male and female rat pups from 11 litters were used. All pups were born to Harlan Sprague-Dawley females in the animal colony at the University of Iowa. The pups were raised in litters that were culled to eight pups within 3 d after birth (day of birth = day 0). Litters and mothers were raised in standard laboratory cages (48 × 20 × 26 cm) in which food and water were available ad lib. All animals were maintained on a 12L : 12D schedule with lights on at 6:00 A.M.

Test Environment

The experiment was conducted by placing individual pups inside a double-walled glass chamber (height = 17 cm; inside diameter = 12.5 cm) constructed in the glass shop at the University of Iowa. The double-walled design allowed for the passage of water through the walls of the chamber; by controlling the temperature of the water with a water circulator, T_a inside the chamber could also be controlled. Three access holes in the side of the chamber and a sealed Plexiglas top allowed for the passage of air into and out of the chamber and the passage of thermocouple wires.

A round platform constructed of polyethylene mesh was fitted inside the chamber. When placed on the platform, the pup could move freely on the platform's surface. A small wall around the platform, also constructed of polyethylene, prevented the pups from making contact with the glass walls of the chamber. The mesh allowed for the passage of air from the bottom of the chamber (where it entered) to the top of the chamber (where it was drawn for analysis of oxygen content).

Temperature Measurements

Physiological temperatures and T_a's were measured with chromel-constantan thermocouples (Omega, Stamford, Conn.). Electrical signals from the thermocouples were subjected to cold-junction compensation and fed into a computerized data acquisition system (National Instruments, Austin, Tex.). All thermocouples were calibrated before the experiment in a tem-

perature-controlled water bath with a mercury thermometer accurate to within 0.1°C. T_a in the metabolic chamber was measured with two thermocouples located 4 cm beneath the platform; the two T_a's were averaged on acquisition by the computer.

The two physiological temperatures were measured by attaching thermocouples to the skin surface with collodion as an adhesive (Spiers and Adair 1986; Blumberg and Alberts 1990). Both thermocouples were attached on the midline. One thermocouple was attached in the interscapular region above the brown fat pad, thus providing a measure of interscapular temperature. The second thermocouple was attached in the lumbar region, thus providing a measure of back-skin temperature.

Oxygen Consumption Measurements

Compressed air passed through a two-stage regulator and was split into two lines. One line entered a digital flowmeter (Omega, Stamford, Conn.), was humidified, and was then circulated through the metabolic chamber at 300 mL min^{-1}. After passing through the chamber, the exhaust air was dried and then drawn through one of two channels of an electrochemical oxygen analyzer (Ametek, Pittsburgh, Pa.). The second line of air traveled directly from the air cylinder to the second channel of the oxygen sensor. Oxygen concentration in each airstream was measured simultaneously. The difference in the percentage of oxygen between the chamber's effluent airstream and the nonrespired airstream reflects oxygen consumption by the pup. Specifically, by knowing the airflow rate (i.e., 300 mL min^{-1}) and the pup's weight, oxygen consumption could be calculated. All oxygen consumption values are presented as milliliters of oxygen per kilogram of body weight per minute.

Procedure

On the day of testing, a pup was removed from its cage and placed inside an incubator maintained at 35°–36°C. All test pups were in a postabsorptive state, as evidenced by the presence of milk that was visible through their abdominal skin. After the two thermocouples were attached, the pup was placed inside the metabolic chamber maintained at a thermoneutral T_a (~ 35.5°C). Each pup was given at least 45 min (range: 45–50 min) to acclimate to the chamber. When litter mates were used, they were always assigned to different experimental groups.

After this initial acclimation period, T_a was decreased to either 30.5°C (designated the moderate-temperature group) or 23°C (designated the extreme-temperature group), and the pups were allowed to settle at a new steady state. It was considered that a steady state had been achieved when both interscapular temperature and oxygen consumption had plateaued after the decrease of T_a. Once steady-state readings were recorded for at least 10 min, half of the pups in each group were subjected to positive T_a perturbations, and the remaining pups in each group were subjected to negative T_a perturbations. Then, 13.5–17 min after the start of the perturbation, T_a was returned to its original value of either 30.5°C or 23°C. Pups were monitored for at least 60 min after the start of the perturbation.

During the initial drop in T_a to 30.5°C, pups in the moderate-temperature group required 49–60 min to reach a steady state. In contrast, during the initial drop to 23°C, pups in the extreme-temperature group required 95–116 min to reach a steady state. To control for the shorter period of time required by the moderate-temperature pups and to determine the repeatability of the pups' physiological responses to perturbation, these pups were exposed to a second perturbation that was identical to the first. This second perturbation occurred at least 108–125 min after the first drop from thermoneutrality. After the second perturbation began, pups were again monitored for at least 60 min.

T_a, interscapular temperature, back temperature, and oxygen consumption were measured once every second with a customized data acquisition system for the Macintosh computer (LabView, National Instruments, Austin, Tex.). After the test, the pup was removed from the chamber, its thermocouples were removed, and it was returned to its home cage. After removal of the pup, the oxygen consumption system was allowed to rezero to verify minimal drift in the system over the course of the test.

Statistical Analysis

Data were imported to StatView 4.5 for the Macintosh for statistical analysis. All statistical comparisons were made at the 10-, 20-, 30-, 40-, 50-, and 60-min time points. Paired *t*-tests were used to determine whether a variable's value at a given time point was different from its baseline value at 10 min, and unpaired *t*-tests were used to compare pups in different groups. α was set at 0.05, and a Bonferroni correction procedure was used to adjust α for multiple comparisons. All means are presented with their standard errors.

Results

Body weights for the 16 pups in the experiment ranged from 15.1 to 20.3 g. Mean body weights for the moderate- and extreme-temperature pups were 17.6 ± 0.6 g and 17.7 ± 0.6 g, respectively. These values did not differ significantly.

For the 10-min period before T_a was decreased from 35.5°C, mean interscapular temperature for both the moderate- and extreme-temperature pups was 37.5° ± 0.08°C. For back temperature the respective values were 37.3° ± 0.07°C and 37.3° ± 0.1°C, and for oxygen consumption the respective values were 0.335 ± 0.008 mL kg^{-1} min^{-1} and 0.351 ± 0.012 mL

kg^{-1} min^{-1}. None of the values for the two groups differed significantly.

During the initial decrease in T_a to either 30.5°C or 23°C, the pups exhibited responses similar to those illustrated in Figure 1 (see also Blumberg and Stolba 1996). Of the eight pups in the extreme-temperature group exposed to 23°C, seven increased oxygen consumption to a high level and maintained it at or near that level until T_a was perturbed; for the remaining pup, oxygen consumption decreased approximately 40% from its maximum value before T_a was perturbed.

During the 10-min preperturbation baseline period, mean T_a's for the moderate- and extreme-temperature groups were 30.6° ± 0.03°C and 23.0° ± 0.03°C, respectively. Over this same 10-min period, mean interscapular temperatures for the two respective groups were 36.7° ± 0.24°C and 33.0° ± 0.3°C ($t_{14} = 9.39$, $P < 0.0001$). The respective means for back temperature were 35.6° ± 0.2°C and 30.7° ± 0.3°C ($t_{13} = 13.31$, $P < 0.0001$), and for oxygen consumption the respective means were 0.549 ± 0.023 and 0.725 ± 0.028 mL kg^{-1} min^{-1} ($t_{14} = 4.87$, $P < 0.0002$).

The 10-min baseline period began once it appeared that a pup's interscapular temperature and oxygen consumption had plateaued after the initial decrease in T_a. Pups in both groups exhibited very little variability in interscapular temperature, back temperature, and oxygen consumption. Specifically, the mean range of interscapular temperature over the 10-min baseline period was 0.2° ± 0.01°C for the moderate-temperature pups and 0.3° ± 0.02°C for the extreme-temperature pups, an extremely small difference that nonetheless was statistically significant ($t_{14} = 2.7$, $P < 0.02$). The mean ranges of back temperature were 0.2° ± 0.05°C and 0.3° ± 0.03°C, and for oxygen consumption the mean ranges were 0.057 ± 0.007 and 0.082 ± 0.013 mL kg^{-1} min^{-1}, respectively. None of these values differed significantly. Thus, the physiological measures for pups in both groups had plateaued before the perturbation protocol began.

The values of interscapular temperature, back temperature, oxygen consumption, and T_a for the two groups of moderate-temperature pups that experienced either positive or negative T_a perturbations are presented in Figure 2. It can be seen that as T_a was perturbed, interscapular temperature did not deviate far from its initial baseline value. This resistance to perturbation was related to compensatory changes in oxygen consumption that reflect modulation of BAT thermogenesis. Back temperature more closely mirrored the changes in T_a than did interscapular temperature because of the greater distance of the back temperature measurement site from the interscapular depot of BAT.

The physiological responses of moderate-temperature pups to a second identical perturbation are not shown in Figure 2 because they were very similar to those seen during the first perturbation. Paired *t*-tests were used to test for significant differences between the two successive perturbations at the moderate T_a. At no 10-min time point and for no variable did the two perturbations differ significantly from each other. It can be concluded that a prolonged period in the cold and multiple challenges do not reduce thermogenic response, as has been shown by others for as long as 8 h after maternal separation (e.g., Spiers and Adair 1986). Thus, in comparing the moderate- and extreme-temperature groups below, only the data for the first perturbation of the moderate-temperature pups will be discussed.

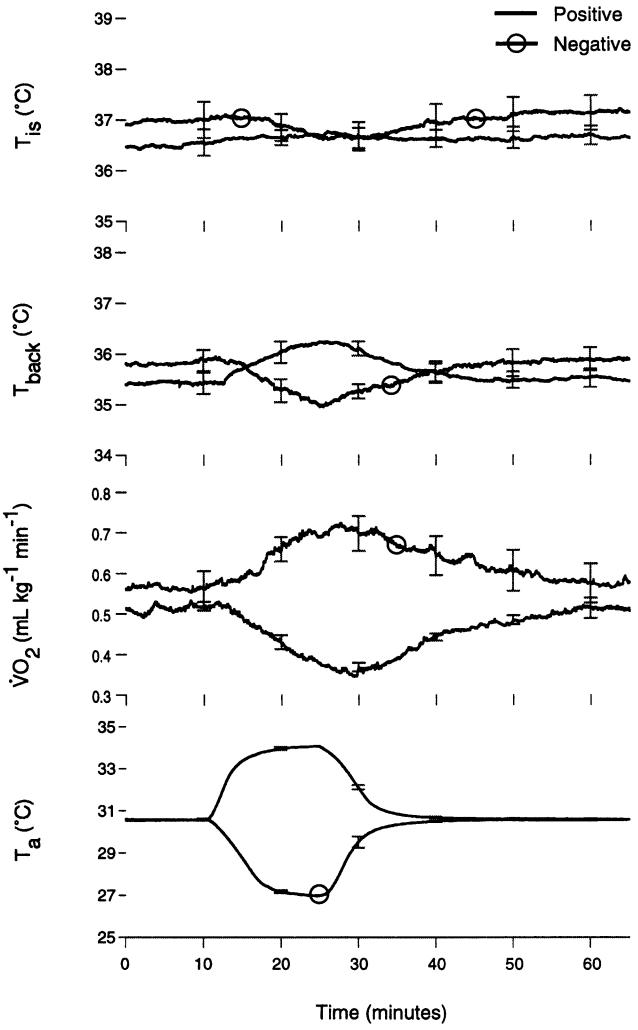

Figure 2. Mean values of interscapular temperature (T_{is}), back temperature (T_{back}), oxygen consumption ($\dot{V}O_2$), and T_a for pups in the moderate-temperature group experiencing either positive ($n = 4$; two males, two females) or negative ($n = 4$; two males, two females) T_a perturbations. Data loss occasionally reduced n to 3. Data are presented as mean ± standard error of the mean (SEM).

In contrast to moderate-temperature pups, extreme-temperature pups had already maximized oxygen consumption at the T_a of 23°C and thus were not able to modulate heat production during the T_a perturbation (Fig. 3). This resulted in relatively large changes in interscapular temperature and back tempera-

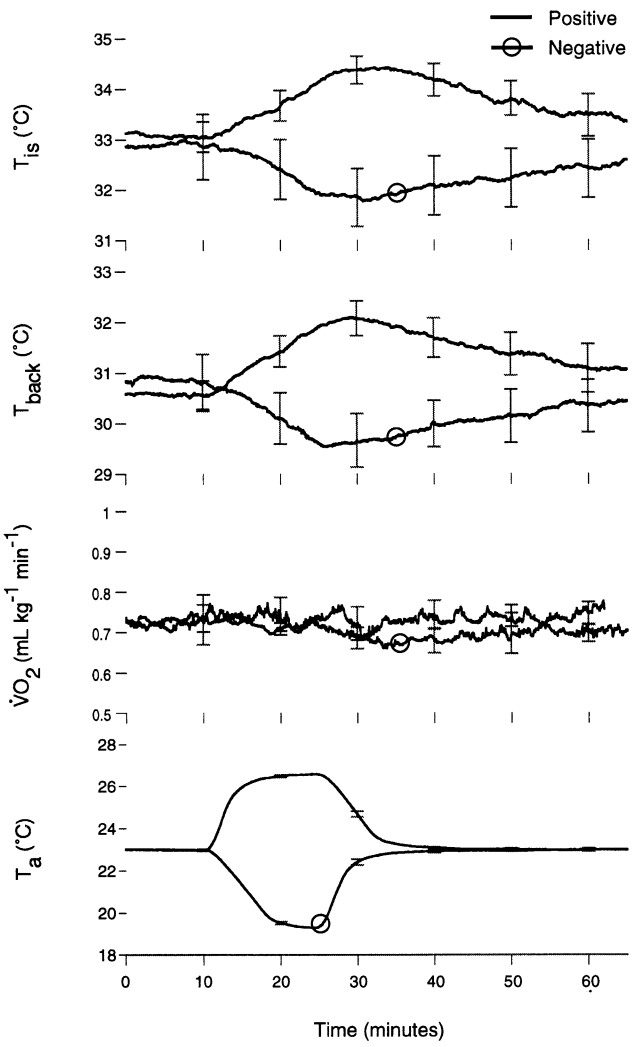

Figure 3. Mean values of interscapular temperature (T_{is}), back temperature (T_{back}), oxygen consumption ($\dot{V}O_2$), and T_a for pups in the extreme-temperature group experiencing either positive (n = 4; two males, two females) or negative (n = 4; three males, one female) T_a perturbations. Data loss occasionally reduced n to 3. Data are presented as mean ± SEM.

ture that mirrored the changes in T_a. Moreover, the effect of the perturbation was greater than that for the moderate-temperature pups, as can be seen from the long length of time required for these values to return to baseline.

As can be seen in Figures 2 and 3, the positive and negative T_a perturbations produced changes in the measured variables that were similar in magnitude but different in sign. Thus, in order to perform statistical comparisons between the moderate- and extreme-temperature groups, the positive and negative perturbation data for all eight pups in both groups were collapsed by means of the following procedure: First, the mean for each variable over the 10-min baseline period was calculated. Next, for each second of the test, a delta score was calculated by computing the difference between each variable and its mean baseline value. Finally, the absolute values of each delta score were determined in order to equilibrate data for pups experiencing positive and negative perturbations. Thus, this procedure provides an absolute delta score for each second and for each variable throughout the test. These data are presented in Figure 4.

It is clear from Figure 4 that T_a was perturbed similarly in both experimental groups. Specifically, the maximum absolute deviations in T_a from baseline were 3.6° ± 0.04°C for the moderate-temperature group and 3.7° ± 0.03°C for the extreme-temperature group. Although this 0.1°C difference was

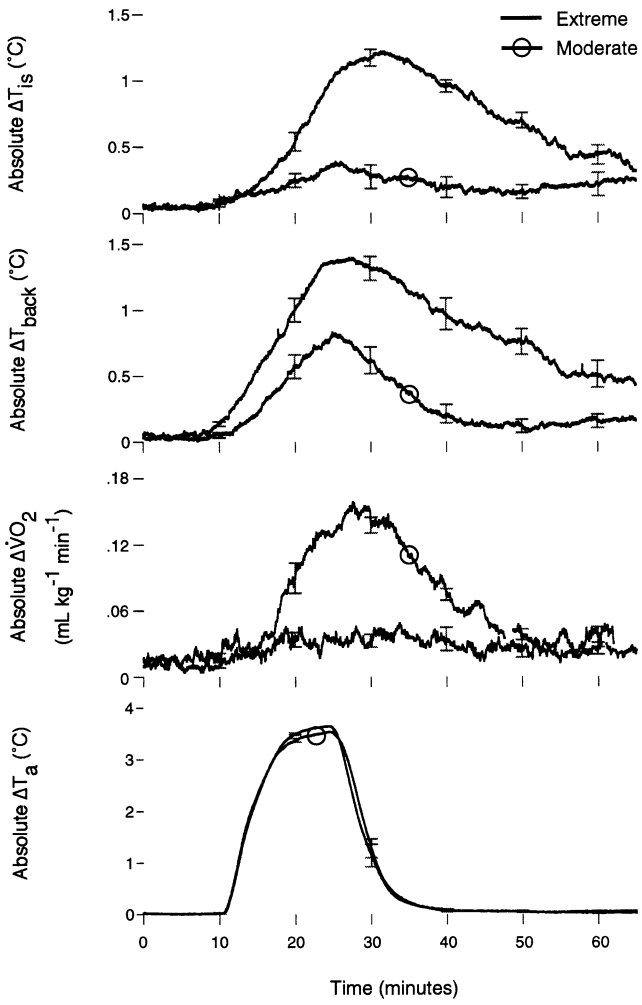

Figure 4. Mean absolute deviations in interscapular temperature (T_{is}), back temperature (T_{back}), oxygen consumption ($\dot{V}O_2$), and T_a throughout the 10-min baseline period and the ensuing perturbation in T_a for the pups in the extreme- and moderate-temperature groups. Deviations for each individual pup were calculated with respect to the mean value over the 10-min baseline period. Mean data (± SEM at 10-min intervals) were calculated for each second of the 65 min of the test presented here; n = 7 or 8 for each point.

statistically significant ($t_{14} = 2.28$, $P < 0.04$), it is not likely that it was physiologically significant, especially in light of the results described below.

The physiological responses of pups to T_a perturbation differed substantially between experimental groups. For the extreme-temperature group, interscapular temperature was significantly different from baseline at every succeeding time point ($3.94 \leq t_7 \leq 11.95$, $P < 0.006$). In contrast, for the moderate-temperature group, interscapular temperature did not deviate far from baseline throughout the test. The mean difference from baseline ranged from only 0.1° to 0.2°C, although these differences did approach statistical significance at the 20-, 30-, and 40-min time points ($2.32 \leq t_{6-7} \leq 2.66$, $0.03 \leq P \leq 0.06$). By the 50- and 60-min time points, interscapular temperature had clearly returned to baseline ($1.37 \leq t_7 \leq 1.84$, $P \geq 0.11$). Finally, differences in interscapular temperature between the two groups were significant at the 20- through the 50-min time points ($3.41 \leq t_{13-14} \leq 8.76$, $P < 0.005$) but not at the 60-min time point ($t_{14} = 2.08$, $P > 0.05$).

The data for back temperature in Figure 4 indicate that, as with interscapular temperature, pups in the extreme-temperature group were perturbed greater than were pups in the moderate-temperature group. Values of back temperature differed between the two groups at the 30- through the 60-min time points ($3.03 \leq t_{13} \leq 5.60$, $P < 0.01$). Nonetheless, back temperature did deviate appreciably during the perturbation in the moderate-temperature group, differing significantly from baseline at the 20- and 30-min time points ($4.86 \leq t_6 \leq 4.99$, $P < 0.003$), but not thereafter. In contrast, for the extreme-temperature group, back temperature deviated significantly from baseline at the 20- through the 60-min time points ($5.66 \leq t_6 \leq 11.72$, $P < 0.002$).

Finally, while oxygen consumption for the moderate-temperature group increased significantly over baseline at the 20-, 30-, and 40-min time points ($5.35 \leq t_6 \leq 22.64$, $P < 0.002$), oxygen consumption for the extreme-temperature group never deviated significantly from baseline ($1.05 \leq t_7 \leq 1.92$, $P > 0.09$). Oxygen consumption differed between the two groups at the 20-, 30-, and 40-min time points ($3.24 \leq t_{13} \leq 11.72$, $P < 0.007$).

Discussion

The present results show that BAT thermogenesis responds to T_a perturbation differently depending on the initial conditions of the experiment. Specifically, during perturbations from a moderate T_a of 30.5°C, interscapular temperature deviated very little from baseline and returned to baseline quickly. The resistance of interscapular temperature to perturbation at the moderate T_a was accomplished by compensatory changes in oxygen consumption, reflecting active modulation of BAT thermogenesis. In contrast, during perturbations from an extreme T_a of 23°C, interscapular temperature deviated significantly from baseline and returned to baseline slowly. Not surprisingly, these changes in interscapular temperature could not be resisted because BAT thermogenesis had already been stimulated beyond its maximum capability. All together, with the definition of relative stability described earlier, these results suggest that BAT thermogenesis is relatively stable during moderate cold exposure. In addition, the data support the hypothesis that interscapular temperature (or a correlated variable; see below) is regulated during moderate cold exposure (Blumberg and Stolba 1996).

Regulation of interscapular temperature is perhaps most strongly supported by the data for the moderate-temperature pups during positive T_a perturbation. Although moderate cooling to a T_a of 30.5°C resulted in decreased values of interscapular temperature and back temperature as well as increased BAT thermogenesis, the increase in T_a during the perturbation resulted in an immediate decrease in BAT thermogenesis before the pups had benefited substantially from the warmth provided (Fig. 2). Moreover, the metabolic response to the positive perturbation was the mirror image of the response to the negative perturbation, a surprising observation that further suggests that pups were defending interscapular temperature at the moderate T_a. That interscapular temperature may be defended at a level lower than that observed at a thermoneutral T_a (e.g., 35.5°C) is not inconsistent with the suggestion that this system is behaving homeostatically (see Mrosovsky 1990).

Neonatal rats have often been referred to as poikilotherms (e.g., Fowler and Kellogg 1975), a designation that reflects an emphasis on the inability of neonates to maintain core temperature (i.e., usually rectal temperature) at a given set point in the cold. As noted by Nedergaard et al. (1986), however, it is increasingly being appreciated that the apparent poikilothermy of newborns often reflects their exposure to extreme cold or the neglect of behavioral mechanisms. In addition, we believe that the traditional reliance on rectal temperature as the metric by which successful neonatal thermoregulation is judged (e.g., Bertin et al. 1993) diverts our attention from the regulatory processes taking place. After all, it should be remembered that blood warmed by BAT is directed primarily toward the vital organs of the thoracic cavity (especially the heart; Smith 1964), which suggests that the regulation of specific organ temperatures may be the primary concern of this system. The recent finding that modulation of BAT thermogenesis in the cold is closely related to the maintenance of heart rate supports this notion (Blumberg et al. 1997). Such compartmentalization of thermoregulation would be analogous to the selective regulation of brain temperature in mammals (Hayward and Baker 1969), of brain and eye temperatures in sharks (Block and Carey 1985), and of thoracic temperature in bumblebees (Heinrich 1993).

Because interscapular temperature changed very little during perturbation at the moderate T_a, it does not seem likely that interscapular temperature itself could provide the relevant in-

formation for effecting the thermogenic response to perturbation. Alternatively, skin temperature at other locations that are not adjacent to the source of heat production (e.g., back temperature) could provide such information. These thermal inputs could arrive through the spinal cord from thermal sensors throughout the body trunk and limbs (Brück and Wünnenberg 1970) and through the trigeminal nerve from thermal sensors in the facial region (Dickenson et al. 1979). Any or all of these skin inputs, in addition to sensors in the body core and brain, could contribute to the modulation of BAT thermogenesis.

Autonomic thermoregulation in adult mammals is a complex process involving an array of regulatory components (e.g., shivering and nonshivering thermogenesis, piloerection, and vasoconstriction) organized at multiple levels of the neuraxis (Satinoff 1978). The BAT thermogenic system of the neonatal rat functions in virtual isolation from these other components (since they are still undeveloped) and thus provides the experimenter with a unique opportunity to investigate the rules that govern its function. Using the present findings as a foundation for understanding this single homeostatic component, we can perhaps begin to develop a broader understanding of the regulatory principles that govern the more complex and interactive systems of adults.

Acknowledgments

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