

Brown fat thermogenesis and cardiac rate regulation during cold challenge in infant rats

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Blumberg, Mark S., Greta Sokoloff, and Robert F. Kirby. Brown fat thermogenesis and cardiac rate regulation during cold challenge in infant rats. *Am. J. Physiol.* 272 (*Regulatory Integrative Comp. Physiol.* 41): R1308–R1313, 1997.—Infants rats depend on heat production by brown adipose tissue (BAT) during cold challenge. Although it has been suggested that BAT thermogenesis protects the heart in the cold, the relationship of BAT activation to cardiac rate has not been examined directly. In the first experiment, the cardiac rate of 2- and 7- to 8-day-old rat pups was monitored during moderate and extreme cold challenge. Pups at both ages maintained cardiac rate during moderate cold challenge while BAT thermogenesis was increasing. In contrast, cooling to air temperatures at which BAT thermogenesis could increase no further resulted in pronounced bradycardia. In the second experiment, ganglionic blockade was used to eliminate BAT heat production and autonomic control of the heart in 7- to 8-day olds. Blockade suppressed BAT thermogenesis in the cold and led to pronounced decreases in interscapular temperature and cardiac rate. These data suggest that cardiac rate in infant rats is modulated both by the autonomic nervous system and BAT thermogenesis.

nonshivering thermogenesis; thermoregulation; autonomic nervous system

BROWN ADIPOSE TISSUE (BAT) is the primary or exclusive means of heat production in the newborns of many mammalian species, including rats and humans (5, 15, 22, 25). More than 30 years ago, as investigators were first learning of the thermogenic function of BAT, Smith (21) noted that BAT applies "its metabolic heat directly to the blood stream as this returns to the thorax; the vital structures are thus protected from undue cooling" (p. 1689). Moreover, the "direct venous connection between interscapular brown fat and the azygous vein could be readily adduced as indicative of a direct convective heat transfer to the heart" (23, p. 146).

Extreme changes in temperature affect cardiac rate, both *in vivo* and *in vitro* (1, 9, 10, 17). The classic investigations of this phenomenon in infant mammals (1, 10), however, were performed before the function of BAT was known and before the significance of using moderate thermal challenges was appreciated (7). By using moderate thermal challenges to investigate infant thermoregulation, previously hidden capabilities were revealed. In week-old rats, for example, BAT thermogenesis increases progressively from a minimum level at an air temperature of 35°C to a maximum level at air temperatures just 9°C lower: any further decrease in air temperature fails to elicit higher levels of BAT thermogenesis and results in accelerated bodily cooling (4, 24, 25). Thus our current understanding of the capabilities and limitations of BAT thermogenesis in infant rats provides the opportunity to examine the

relationship between BAT thermogenesis and cardiac rate.

In one experiment, we measured thermoregulatory responses and cardiac rate during varying levels of cold exposure in 2- and 7- to 8-day-old rats. Pups at these two ages rely solely on BAT for heat production and exhibit different sensitivities to varying levels of cooling (4). In a second experiment, 7- to 8-day-old rats were tested during cold challenge after ganglionic blockade to inhibit BAT thermogenesis and to isolate the heart from sympathetic and parasympathetic control. These experiments suggest that BAT's thermogenic function is directed in part toward the selective control of heart temperature and, in turn, the maintenance of cardiac function during cold challenge.

METHODS

Subjects. A total of 15 male rat pups from 12 litters was used: five 2-day-old and five 7- to 8-day-old pups in the first experiment, and five 7- to 8-day-old pups in the second experiment. At the time of testing, the 2-day-old rats weighed between 6.4 and 9.8 g, and the 7- to 8-day-old rats weighed between 17.2 and 21.2 g. 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 days after birth (day of birth = *day 0*). Litters and mothers were housed in standard laboratory cages (48 × 20 × 26 cm) in which food and water were available *ad libitum*. All animals were maintained on a 12:12-h light-dark schedule with lights on at 0600.

Test environment. All experiments were conducted by placing individual pups inside a double-walled glass chamber (height = 17 cm; ID = 12.5 cm). Air temperature (T_a) within the chamber was controlled by pumping temperature-controlled water through the walls of the chamber. Access holes and connectors in the side of the chamber and the lid allowed for the passage of air into and out of the chamber as well as the passage of thermocouple wires and electrocardiogram (ECG) leads.

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 (diameter = 12 cm). 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 unobstructed flow of air through the chamber.

Temperature measurements. Physiological and air temperatures were measured using chromel-constantan thermocouples (Omega, Stamford, CT). Electrical signals from the thermocouples were subjected to cold-junction compensation and fed into a computerized data-acquisition system (National Instruments, Austin, TX). All thermocouples were calibrated before the experiment in a temperature-controlled water bath using a mercury thermometer accurate to within 0.1°C. T_a within the metabolic chamber was measured using two thermocouples located beneath the platform; the two T_a values were averaged on acquisition by the computer. Physi-

ological temperatures were attained by attaching thermocouples to the skin surface using collodion as an adhesive (4, 25). Thermocouples were attached on the midline. One thermocouple was attached in the interscapular region above the BAT pad, thus providing a measure of interscapular temperature (T_{is}). In the chlorisondamine-treated pups, a second thermocouple was attached in the lumbar region distant from the BAT pad, thus providing a measure of back temperature (T_{back}).

Oxygen-consumption measurements. Compressed air passed through a two-stage regulator and was split into two lines. One line passed through a digital flowmeter (Omega), was humidified, and was then circulated through the metabolic chamber at 300 ml/min. Exhaust air from the chamber 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, and the percent difference in concentration was computed to 0.001%. This percent difference was fed into the data-acquisition computer and transformed into a measure of oxygen consumption in milliliters of O_2 per kilogram per minute. Oxygen consumption was not corrected for respiratory exchange ratios less than unity because it leads to a systematic underestimation of oxygen consumption of only 5% during normoxia in newborn rats (11).

Data acquisition. For both experiments, thermal and oxygen-consumption measures were acquired at least twice each minute using a customized data-acquisition system for the Macintosh computer (LabView; National Instruments). A second data-acquisition system was used to acquire ECG data simultaneously at the rate of 1,000/s.

Procedure. On the day of testing, a pup was removed from its cage, weighed, and anesthetized with ether. After ~1 min of exposure to the ether, the pup was placed inside an incubator maintained at 35–36°C. Two or three ECG leads were implanted transcutaneously. Collodion was used to secure the electrodes and to improve the electrical connection. The ECG leads from the pup were connected through the chamber lid to a differential amplifier (A-M Systems, Everett, WA). The signal was filtered and amplified before being acquired by the computer.

Before testing, all pups were in a postabsorptive state, as evidenced by the presence of milk visible through their abdominal skin. After the thermocouples were attached, the pup was placed inside the metabolic chamber maintained between 34.5 and 36°C. Each pup was given at least 45 min to acclimate to the chamber, after which cardiac rate data were acquired for 1 min. Air temperature was then decreased in succession to 32.5, 30, 26, and 21°C for the 2-day-old rats and 30, 27, 23, and 17°C for the 7- to 8-day-old rats. Pups were given at least 45 min to stabilize at each temperature, at which time cardiac rate data were acquired.

In a second experiment, five 7- to 8-day-old pups were injected with chlorisondamine hydrochloride (Ciba-Geigy, Summit, NJ) ~25 min after being placed in the metabolic chamber. The drug was dissolved in isotonic saline and injected subcutaneously at a dose of 5 mg/kg and a volume of 1 μ l/g body wt; this dose is effective in blocking ganglionic neurotransmission in infant rats (20). At least 15 min after the injection, the first cardiac rate reading was taken, followed by successive air temperature decreases to 30, 27, and 23°C, separated by an interval of at least 45 min. Cardiac rate data were acquired ~15 and 45 min after the start of each decrease in T_a .

After each test, the pup was removed from the chamber, its ECG leads and thermocouples were removed, and it was returned to its home cage. After removal of the pup from the metabolic chamber, the oxygen-consumption system was allowed to rezero to verify minimal drift in the system over the course of the test.

Data analysis. Thermal and metabolic measures were imported into StatView 4.5 for the Macintosh, and cardiac rate data were imported into DataDesk 5.0. A scatterplot of the cardiac rate data was produced for each session, and each point in the scatterplot could be linked to a row number that represented the passage of 0.001 s. The row numbers corresponding to the peaks of successive R waves were then determined for as many clear records as possible. The inter-beat intervals (IBI) were then determined, and mean IBI was calculated for each pup at each phase of the experiment. These means were calculated from a range of 59–312 IBIs. Paired *t*-tests were used to determine whether a given variable had changed from its value at the previous time point; α was set at 0.05, and a Bonferroni correction procedure was used to adjust α for multiple comparisons.

RESULTS

As shown in Fig. 1, when T_a was decreased to 32.5 or 30°C, 2-day-old pups were able to maintain T_{is} by increasing BAT thermogenesis, as reflected in the increase in oxygen consumption. Then, when T_a was decreased further to 26 and 21°C, BAT thermogenesis could increase no further, as reflected in the successive decreases in oxygen consumption at these two air temperatures as well as the accelerated decreases in T_{is} .

Figure 1 also presents mean IBI at each phase of the experiment. It can be seen that mean IBI changed very little at air temperatures between 36 and 30°C. In contrast, mean IBI increased significantly when T_a was decreased below 30°C.

Similar results were obtained with the 7- to 8-day-old rats, except only the final decrease in T_a to 17°C resulted in a significant decrease in oxygen consumption, which was accompanied by an accelerated decrease in T_{is} (Fig. 2). Changes in IBI mirrored the responses in oxygen consumption and T_{is} , with only the final decrease in T_a eliciting a significant increase in IBI. Thus a 12°C decrease in T_a from 35 to 23°C had little effect on IBI, whereas a 6°C decrease from 23 to 17°C resulted in a >50% increase in IBI.

Ganglionic blockade abolished BAT thermogenesis in the 7- to 8-day-old rats, as evidenced by suppressed oxygen consumption and steadily decreasing T_{is} at each phase of the experiment (Fig. 3). The difference between T_{is} and T_{back} remained small and constant throughout the test, which is consistent with suppression of BAT thermogenesis (4). Also consistent with this conclusion, oxygen consumption decreased steadily throughout the test, reflecting a generalized cold-induced depression of cellular metabolism (5). Finally, in the absence of BAT thermogenesis and neural control of the heart, IBI increased steadily so that, by the end of the experiment, it had increased ~300% over baseline levels.

Thus far, the data suggest a relationship between T_{is} and IBI. To better assess the nature of the relationship

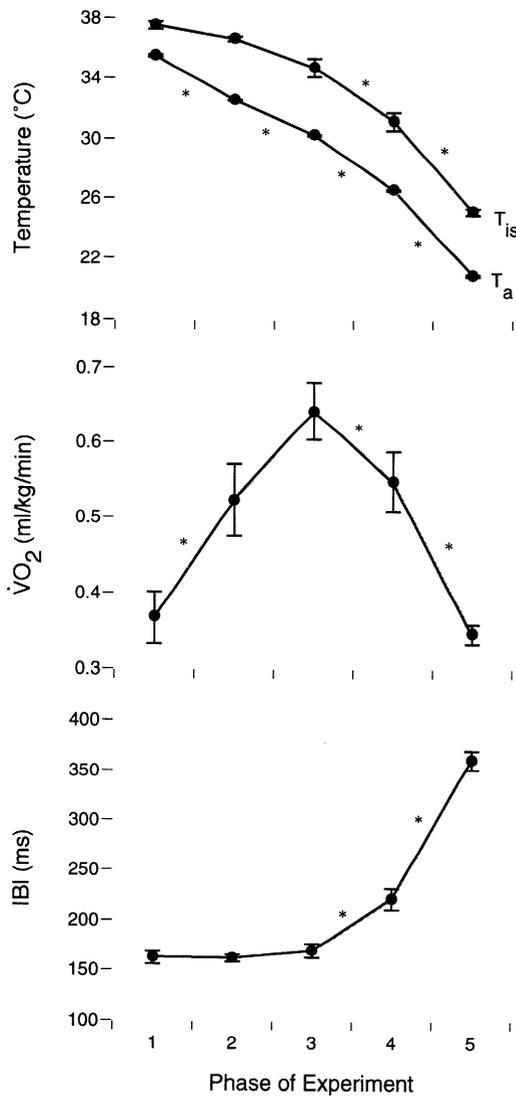


Fig. 1. Mean values of air temperature (T_a), interscapular temperature (T_{is}), volume of inspired oxygen ($\dot{V}O_2$), and interbeat interval (IBI) for 2-day-old rats. Thermal and metabolic measures represent single data points recorded at the time electrocardiogram (ECG) data were acquired. ECG data were acquired over a 1-min recording period. $n = 5$ for all points, except $n = 4$ for the 5th reading of IBI. Data given as means \pm SE. * $P < 0.0125$, significantly different from its previous value, paired t -test.

between these two variables, they are plotted against each other in Fig. 4. Because many rate processes increase exponentially with respect to temperature (18), the mean IBIs were log-transformed before analysis.

The data for the three experimental groups were analyzed using linear and curvilinear regression. All data contributed by each pup at each T_a were included in these analyses. Because the inclusion of multiple data points from each pup in a regression analysis violates statistical assumptions of independence, we conducted parallel analyses in which 1) linear and curvilinear regressions were performed on group mean data at each T_a and 2) linear regressions were performed on the data for each pup and t -tests were used to determine whether the mean slopes for each group

deviated significantly from 0. Because these analyses yielded results very similar to those reported below, they will not be discussed further.

The 2- and 7- to 8-day-old rats maintained low IBIs for values of T_{is} ranging from ~ 34 to 38°C (Fig. 4). Below this range, however, IBI increased progressively. For the 2-day-old rats, although linear regression yielded a highly significant result ($r^2 = 0.943$, $F_{1,22} = 363.9$, $P < 0.0001$), residual analysis indicated that curvilinear regression was more appropriate; polynomial regression of degree 2 yielded a highly significant result ($r^2 = 0.966$, $F_{2,21} = 295.1$, $P < 0.0001$).

For the 7- to 8-day-old rats, the linear regression for the T_{is} and IBI data was also highly significant ($r^2 = 0.863$, $F_{1,23} = 145.2$, $P < 0.0001$). Residual analysis again indicated that a curvilinear regression is more appropriate, and the resulting polynomial regression of

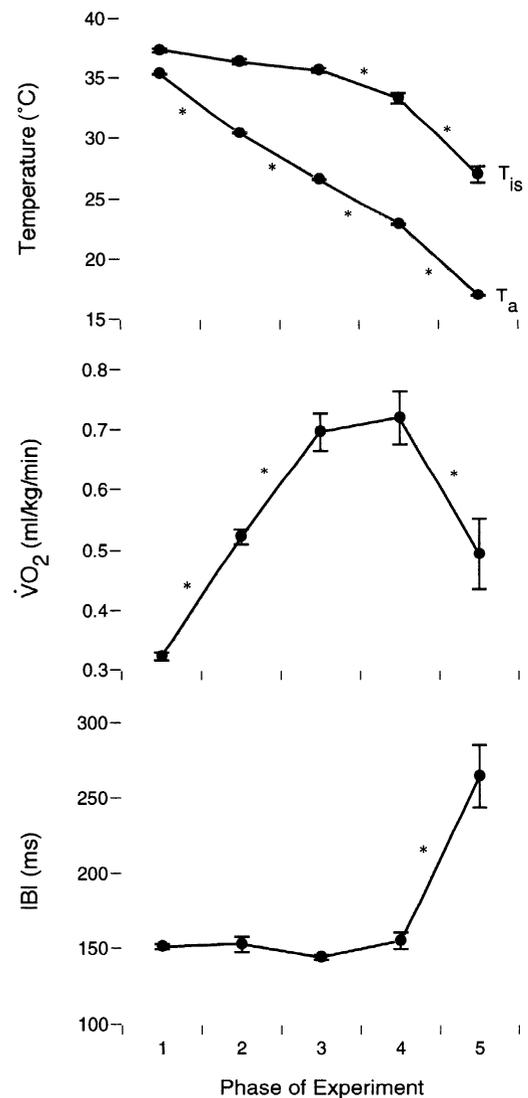


Fig. 2. Mean values of T_a , T_{is} , $\dot{V}O_2$, and IBI for 7- to 8-day-old rats. Thermal and metabolic measures represent single data points recorded at the time ECG data were acquired. ECG data were acquired over a 1-min recording period. $n = 5$ for all points. Data given as means \pm SE. * $P < 0.0125$, significantly different from its previous value, paired t -test.

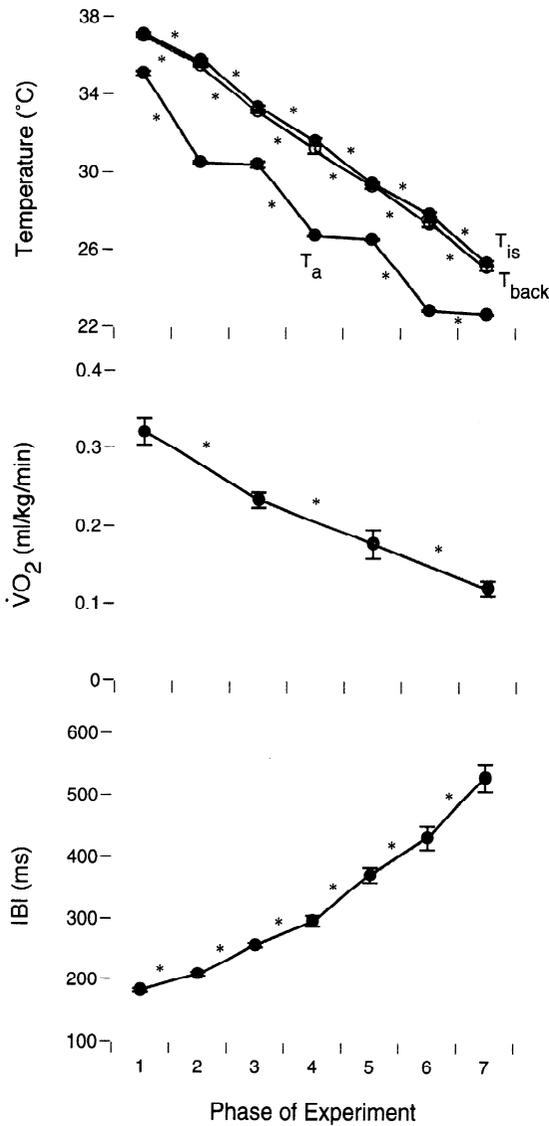


Fig. 3. Mean values of T_a , T_{is} , back temperature (T_{back}), $\dot{V}O_2$, and IBI for 7- to 8-day-old rats injected with chlorisondamine. Thermal and metabolic measures represent single data points recorded at the time ECG data were acquired. Because of the response lag in the $\dot{V}O_2$ system, data for the 15-min time points after each decrease in T_a are not included. ECG data were acquired over a 1-min recording period. $n = 5$ for all points. Data given as means \pm SE. * $P < 0.008$, significantly different from its previous value, paired t -test.

degree 2 was highly significant ($r^2 = 0.963$, $F_{2,22} = 287.9$, $P < 0.0001$).

The relation between \log IBI and T_{is} for the chlorisondamine-treated 7- to 8-day-old rats is also shown in Fig. 4. For these data, residual analysis indicated that linear regression was appropriate, and the resulting analysis was highly significant ($r^2 = 0.980$, $F_{1,33} = 1,649.2$, $P < 0.0001$).

At any given interval, the slopes of the lines in Fig. 4 are proportional to the rate at which IBI increases with decreasing T_{is} . This rate value is often expressed as Q_{10} , a term that denotes a factorial change in a variable for a given 10°C change in temperature (18). Table 1 presents the Q_{10} values for each group at each phase of the experiment. For both the 2- and 7- to 8-day-old rats, Q_{10} increased as T_{is} decreased, so that, by the final

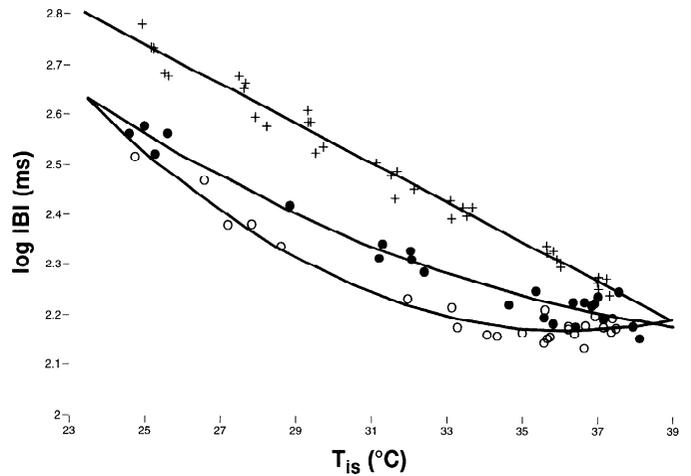


Fig. 4. \log IBI vs. T_{is} for the untreated 2-day-old rats (\bullet ; $n = 24$) and 7- to 8-day-old rats (\circ ; $n = 25$) and the chlorisondamine-treated 7- to 8-day-old rats ($+$; $n = 35$). An increasing value on the y-axis indicates a slowing of cardiac rate. Best-fit polynomial functions of degree 2 are shown for the untreated pups at both ages; the data for the chlorisondamine-treated pups are fit with a linear function.

phase of the experiment, Q_{10} exceeded values of 2 in both age groups. These findings are consistent with the conclusion that pups are able to modulate cardiac rate independently of temperature during moderate thermal challenges, but, as air temperature decreases further, cardiac rate becomes increasingly dependent on temperature. In contrast, the data for the chlorisondamine-treated 7- to 8-day-old rats indicate a relatively stable dependence of IBI on temperature at all phases of the experiment; specifically, Q_{10} ranged from 2.28 to 2.87 throughout the experiment. Such values are typical of temperature-dependent rate processes (5, 18).

Table 1. Q_{10} as calculated from mean T_{is} and mean IBI for each experimental group and for each phase of the experiment

Group	Mean T_{is} , $^\circ\text{C}$	Mean IBI, ms	Q_{10}
2-day-old Rats	37.5	162.2	
	36.6	161.7	0.97
	34.7	169.2	1.27
	31.1	221.2	2.11
	25.1	360.3	2.26
7- to 8-day-old Rats	37.2	151.0	
	36.3	152.5	1.12
	35.6	144.3	0.45
	33.3	154.8	1.36
	27.0	264.1	2.34
7- to 8-day-old Rats injected with chlorisondamine	37.1	182.4	
	35.8	209.2	2.87
	33.3	257.1	2.28
	31.6	296.0	2.29
	29.4	370.9	2.78
	27.8	430.7	2.54
	25.3	528.7	2.27

Q_{10} was calculated according to the following formula: $Q_{10} = (IBI_{[2]}/IBI_{[1]}) [10/(T_{is[2]} - T_{is[1]})]$, where the bracketed subscripts denote successive phases of the experiment (18). Q_{10} , factorial change in a variable for a given 10°C change in temperature; T_{is} , interscapular temperature; IBI, interbeat interval.

DISCUSSION

These experiments demonstrate that the ability of infant rats to maintain cardiac rate during thermal challenge is correlated with their ability to modulate BAT thermogenesis. Specifically, both 2- and 7- to 8-day-old pups maintained cardiac rate during moderate thermal challenges to which pups were able to respond with increased BAT thermogenesis. In contrast, when T_a was decreased further and BAT thermogenesis was overwhelmed, T_{is} and cardiac rate also decreased in lockstep. In the second experiment, in which 7- to 8-day-old rats were pretreated with chlorisondamine, a ganglionic blocker that suppresses BAT thermogenesis and blocks autonomic control of the heart, T_{is} and cardiac rate again decreased in a correlated fashion, but now the relation was indicative of a temperature-dependent rate process. All together, these results suggest a role for BAT thermogenesis in the modulation of cardiac rate. Selective manipulation of BAT thermogenesis while assessing cardiac rate will be necessary to demonstrate a direct causal relationship between the two systems.

The difference between the chlorisondamine-treated and untreated 7- to 8-day-old pups in Fig. 4 at any given value of T_{is} reflects the influence of the autonomic nervous system on cardiac rate (27). For the untreated pups, when T_{is} was greater than $\sim 34^\circ\text{C}$, this autonomic influence was effective in regulating cardiac rate independently of T_{is} . When T_{is} decreased in lower air temperatures, however, autonomic activity apparently could not compensate for the temperature-induced depression of cardiac rate: as a result, cardiac rate became increasingly, but not completely, dependent on T_{is} as T_a decreased.

The functional autonomic control of BAT is mediated by the sympathetic nervous system (12), and both anatomic and physiological studies indicate that this tissue is activated by sympathetic terminals in infant rats (3, 8); the suppression of BAT thermogenesis by chlorisondamine in this study is consistent with these earlier findings. In contrast to BAT, the heart receives both sympathetic and parasympathetic innervation, which would be inhibited by ganglionic blockade. Therefore, these results suggest that moderate cold exposure leads to either the elevation of sympathetic drive or the withdrawal of parasympathetic drive to the heart. The elevation of sympathetic drive to the heart could be mediated either by direct terminal release or circulating catecholamines from the adrenal medulla (16, 27).

The present results lead us to suggest that the combination of BAT thermogenesis and autonomic control of the heart allows infant rats to maintain cardiac rate across a wider range of T_a values than otherwise would be possible. Cardiac rate plays a dominant role in the maintenance of cardiac output, especially in younger animals, because of the diminished ability to regulate myocardial contractility directly (19, 26). Therefore, the maintenance of cardiac rate along with an increase in respiratory rate (24) would help pups sustain adequate tissue perfusion during moderate

cold challenge. However, the decline in cardiac and respiratory rates during extreme cold challenge when BAT thermogenesis is overwhelmed may necessitate the recruitment of other hemodynamic adjustments, such as increased preload to the heart by elevating central venous pressure, to maintain cardiac output to meet tissue needs (29). Overall, the changes in cardiac output and respiratory rate would work in concert with the reappportionment of blood flow resulting from alterations in systemic vascular resistance (28).

Perspectives

Investigators of thermoregulation across many vertebrate and invertebrate species have provided us with numerous examples of the selective thermal regulation of organs and bodily compartments. Prominent examples include the selective warming of the eye and brain of swordfish and many billfishes (2, 6) and the selective regulation of brain temperature in many mammalian species (13) and of thoracic temperature in bumblebees (14). The regionally specific distribution of BAT throughout the bodies of the infants and adults of many mammalian species suggest that this thermogenic tissue provides focal warming to the heart, cervical spinal cord, paravertebral ganglia, adrenal glands, and other organs (22). The present findings provide evidence that, for at least the heart, this focal warming has functional consequences for the infant rat's physiological response to cold.

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