Adaptive Thermogenesis Is Intact in B6 and A/J Mice Studied at Thermoneutrality

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To investigate mechanisms of resistance to obesity, the physiologic responses to short-term moderate fat feeding were studied at ambient temperature (T_a) = 23°C and thermonuetrality (T_a = 30°C) in mice susceptible (B6) or resistant (A/J) to obesity. We hypothesized that A/J mice would exhibit greater adaptive thermogenic responses to consumption of moderate-fat diets, and that this response would be attenuated in thermoneutral conditions due to reduced activity of brown adipose tissue (BAT). B6 and A/J mice were adapted to either T_a = 23°C or T_a = 30°C, implanted with telemetry devices, housed in metabolic chambers for measurement of food intake, oxygen consumption (Vo_2), and heart rate (HR), and studied before and during 1 week of consuming a diet containing 32% of calories from fat. Access to 32% fat diet resulted in increased caloric intake in both strains, but caloric intake for A/J mice returned to baseline levels within 72 hours, while B6 mice remained hyperphagic. Both strains exhibited increased light-phase Vo_2 indicative of adaptive thermogenesis; however, there was no strain difference in light-phase Vo_2 during the 1-week feeding trial. Surprisingly, T_a had no effect on diet-induced thermogenesis in either mouse strain. Moderate high-fat feeding produced mild tachycardia that was similar in B6 and A/J mice and more clearly evident at thermonuetrality. We conclude that adaptive thermogenic responses are intact in both mouse strains studied at thermoneutrality, suggesting a minimal role for BAT in the initial metabolic response to hyperphagia. Furthermore, the results suggest that differences in control of caloric intake, rather than capacity for adaptive thermogenesis, may contribute to the relative susceptibility to obesity in A/J and B6 mice.

SEVERAL LINES of evidence support the hypothesis that adaptive thermogenesis, mediated by increases in sympathetic activity, is a critical mechanism of resistance to obesity.[1-4] β-Adrenergic blockade reduces the elevation in oxygen consumption (Vo_2) observed in rats and mice after overfeeding.[1,2] In addition, β-blocker administration in humans can lower metabolic rate and cause weight gain.[3] The lack of resistance to obesity in the $\beta_{1,2,3}$-receptor knockout mouse demonstrates the importance of the sympathetic nervous system mediating obesity resistance.[4] Both rodents[5] and humans[6,7] possess various abilities to engage adaptive thermogenesis that suggests a genetic component to defend body weight. While thermogenic sympathetic activation may provide some protection against obesity, it could mediate concurrent deleterious increases in heart rate (HR) and blood pressure.[8]

The C57BL/6J (B6) and A/J mouse strains are potentially useful for studying genetic differences in obesity resistance. The B6 mouse develops obesity, hyperglycemia, and hyperinsulinemia following long-term access to higher fat diets.[9-14] In contrast, the A/J mouse strain is resistant to obesity over the same period of time, although it has been reported to have similar food intake as the B6 mice.[9-13] This observation suggests potent mechanisms for obesity resistance in A/J mice. Given that sympathetic activation appears to mediate obesity resistance, one purpose of this study was to examine the cardiovascular response to short-term moderate-fat feeding in the A/J and B6 mouse strains.

We have previously demonstrated that ambient temperature (T_a) is an important determinant of food intake, Vo_2, HR, and mean arterial pressure (MAP) in mice, as these parameters are elevated at standard laboratory temperatures (T_a = 23°C) compared to thermoneutrality ($T_a \simeq$ 30°C).[15-17] Thermoneutrality, typically T_a = 28° to 31°C for rodents, is the temperature where energy expenditure to maintain body temperature is at a minimum.[18] The decrease in metabolic rate at thermoneutrality is presumably mediated by decreased sympathetic nervous system activity to brown adipose tissue (BAT).[19-21] BAT is a thermogenic organ that is activated by sympathoexcitation in response to cold and overfeeding in rodents.[3,19,22,23] Thermoneutral housing of mice results in atrophy of BAT[24] and reduced capacity to thermoregulate upon cold exposure.[25] We hypothesized that the thermogenic response to overfeeding in mice would be attenuated at thermoneutrality. Thus, the overall purpose of this study was to elucidate the thermogenic and cardiovascular responses to short-term overfeeding at both T_a = 23°C and T_a = 30°C in the B6 and A/J mouse strains as determined by Vo_2 and HR. We hypothesized that thermogenic responses would be greater in A/J mice compared to B6 mice, and that these responses would be blunted in both strains at thermoneutrality.

MATERIALS AND METHODS

Male B6 (n = 18) and A/J (n = 14) mice obtained from Jackson Labs (Bar Harbor, ME) were housed at either standard laboratory temperatures (T_a = 23°C), or thermoneutrality (T_a = 30°C) for at least 5 weeks before surgery and data collection. At 16 to 24 weeks of age, mice were anesthetized with halothane (1% to 2% in 95% oxygen–5% nitrogen mixture) and surgically instrumented with telemetry devices (TA11PA-C20, Data Sciences International, St Paul, MN) in the right common carotid artery for measurement of cardiovascular function as described previously.[16] A/J mice were treated with atropine (3 mg/kg, subcutaneous) immediately pre- and post-surgery to minimize excessive airway secretions. In spite of this precaution, we experienced lower surgical success rates with A/J mice. In addition to standard chow and water ad libitum, a liquid diet of chocolate

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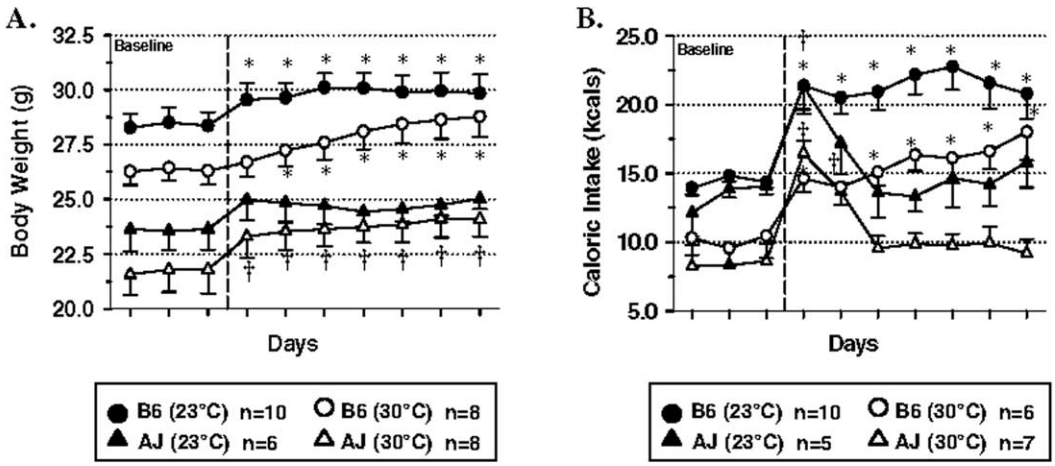

Fig 1. (A) Body weight and (B) caloric intake in B6 (circles) and A/J (triangles) mice during 3 baseline days and 7 days of moderate fat diet at T_a = 23°C (filled symbol) and T_a = 30°C (open symbol). Powdered chow (3.3 kcal/g) was provided ad libitum during baseline, while powdered moderate-fat diet (4.41 kcal/g) was provided ad libitum during the 7-day nutritional intervention. *$P < .05$ *v* baseline for B6 mice; †$P < .05$ *v* baseline for A/J mice. Mice were removed from the food intake analysis (B) if there was consistent placement of food outside the feeder. This is reflected in the n value.

Ensure (Ross, Grove City, OH) was provided for 3 days following surgery. We have found this liquid diet to improve recovery rates in mice, as it is palatable and easy to consume for the mice after surgery. After 3 days, Ensure was no longer provided. Following recovery from surgery (≃7 days) mice were transferred to specially designed cages (18 × 9.5 × 5 inches) and provided ad libitum access to deionized water and powdered chow (Purina 5001, 3.3 kcal/g; Purina Mills, Richmond, IN) contained within a stainless steel feeder that minimized spillage. The cages were placed within previously described environmental chambers[16] that provided computer control of T_a (23°C or 30°C) and the 12-hour light/dark schedule (lights off at 10 PM). Body weight (corrected for transmitter weight of 3.3 g) and food and water consumption were measured daily during the 12th hour (9 to 10 AM to) of the light phase.

The cages were made with a near air-tight seal for continuous measurement of V_{O_2} (mL/min) and carbon dioxide production (V_{CO2}; mL/min) using an approach previously described.[16] Because B6 mice were heavier than A/J mice, V_{O_2} data are reported as both absolute levels (mL/min) and normalized for metabolic mass (mL/min/kg$^{0.75}$) using the Kleiber exponent. Respiratory quotient (RQ; V_{CO_2}/V_{O_2}) was calculated from V_{O_2} and V_{CO_2} data and was not corrected for energy balance. The cage was positioned on the platform with a pivot under its center to determine locomotor activity as previously described.[16] A telemetry receiver positioned under the activity platform was used to determine MAP and HR as described previously.[16]

Mice were acclimated to the experimental cages for 4 to 5 days at the appropriate temperature (T_a = 23°C or T_a = 30°C), before a 3-day baseline recording period. During acclimation and baseline, mice were given ad libitum access to powdered chow (4.5% fat, 3.3 kcal/g; Purina) and deionized water. Following a baseline period mice were given a moderate-fat diet (32% fat from calories, 4.41 kcal/g; Research Diets D12266B, New Brunswick, NJ) ad libitum for 7 days.

Results are reported as means ± SEM. Metabolic data were collected

Table 1. Adjusted Body Weight, Food Intake, and Fluid Intake for 3-Day Baseline Mean, Day 1 and Day 7 Moderate-Fat Diet for B6 and A/J Mice Housed at 23°C and 30°C

	Adjusted Body Weight (g ± SEM)		Food Intake§ (kcal/d ± SEM)		Fluid Intake (g/d ± SEM)	
	B6	A/J	B6	A/J	B6	A/J
23°C	n = 10	n = 6	n = 10	n = 5	n = 10	n = 6
30°C	n = 8	n = 8	n = 6	n = 7	n = 8	n = 8
3-day baseline mean						
23°C	28.4 ± 0.7	23.6 ± 0.9*	14.4 ± 0.3	13.4 ± 0.8	5.7 ± 0.1	4.4 ± 0.2*
30°C	26.1 ± 0.6	21.7 ± 1.0*	9.4 ± 1.3†	9.0 ± 1.1	4.8 ± 0.2	3.7 ± 0.4*
Moderate fat day 1						
23°C	29.6 ± 0.8‡	25.0 ± 0.9*	21.4 ± 1.7‡	21.3 ± 2.0‡	4.7 ± 0.2‡	3.4 ± 0.2*‡
30°C	26.7 ± 0.7	23.4 ± 1.0*‡	14.6 ± 1.0†‡	16.9 ± 0.9‡	5.0 ± 0.1	3.8 ± 0.1*
Moderate fat day 7						
23°C	29.8 ± 0.9‡	25.0 ± 0.5*	20.8 ± 1.8‡	15.8 ± 1.8	3.4 ± 0.4‡	3.4 ± 0.4
30°C	28.8 ± 0.9‡	24.1 ± 0.8*‡	18.0 ± 2.1‡	8.6 ± 0.8*	4.3 ± 0.3	2.7 ± 0.1*‡

*$P < .05$ *v* B6 mice.

†$P < .05$ *v* T_a = 23°C.

‡$P < .05$ *v* baseline.

§Mice were removed from the analysis if there was consistent placement of food outside the feeder. This is reflected in the n value.

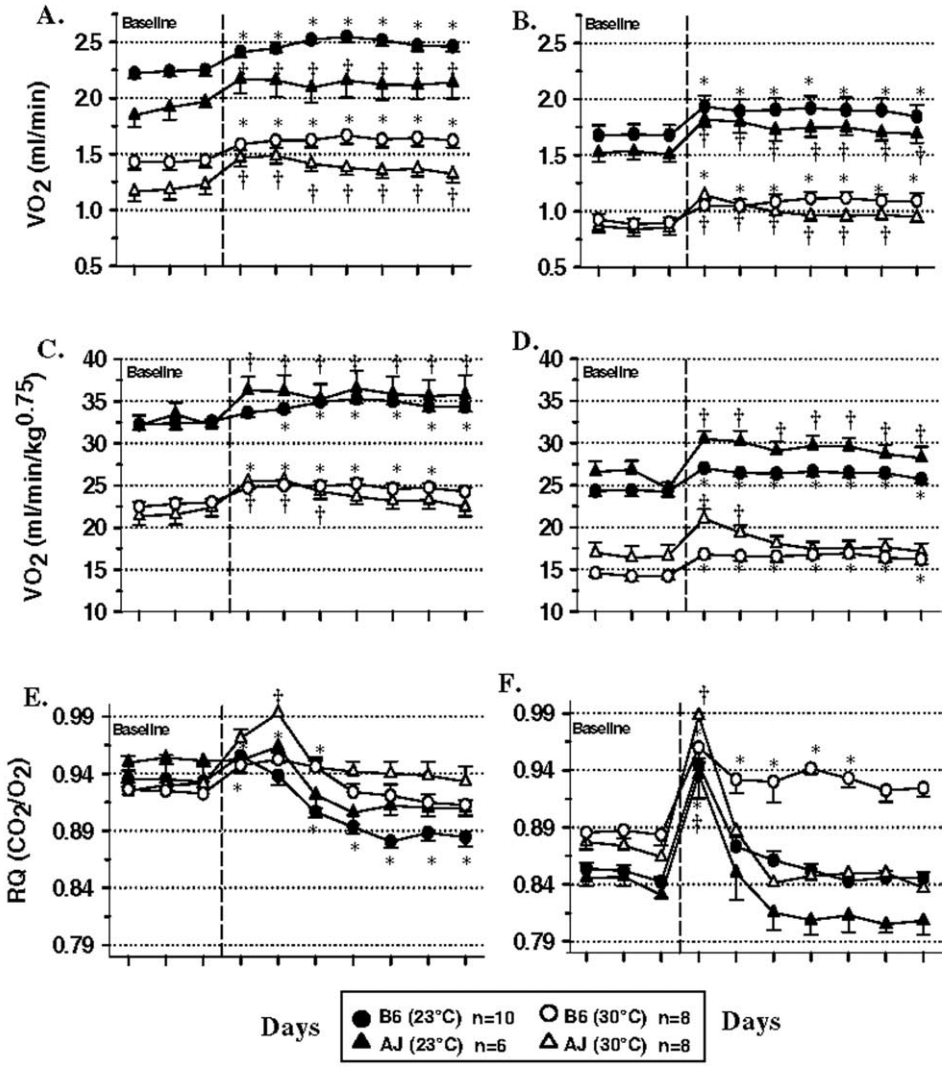

Fig 2. Dark-phase and light-phase absolute Vo_2 (A-dark, B-light), normalized Vo_2 (C-dark, D-light), and RQ (E-dark, F-light) in B6 (circles) and A/J (triangles) mice at T_a = 23°C (filled symbols) and T_a = 30°C (open symbols) during 3 baseline days and 7 days of moderate fat diet. Powdered chow (3.3 kcal/g) was provided ad libitum during baseline, while powdered moderate-fat diet (4.41 kcal/g) was provided ad libitum during the 7-day nutritional intervention. *$P < .05$ *v* baseline for B6 mice; †$P < .05$ *v* baseline for A/J mice.

and stored in 4-minute intervals. Cardiovascular and locomotor activity were collected and stored in 30-second intervals. Average light-phase data were based on 11-hour means (daily maintenance procedures were performed during the last hour of the light cycle), while dark-phase data were based on 12-hour means.

Differences in means between groups were assessed by 1-way analysis of variance (ANOVA). The Scheffé post hoc test was used for comparison between groups when significant F ratios were observed. The effect of moderate-fat diet over time within each respective group was assessed by repeated-measures ANOVA. Tukey's post hoc tests were performed to determine significant differences between means at specific time points following the intervention of moderate fat diet. A 2-way ANOVA was used to analyze delta differences for HR. $P < .05$ was accepted as significant.

RESULTS

Body Weight, and Caloric and Water Intakes

At baseline, B6 mice were heavier than A/J mice, with no effect of T_a on body weight (Fig 1A and Table 1). There were no strain differences in food intake at baseline, although water intake was lower in A/J mice (Table 1). Exposure to thermoneutrality reduced food intake in both strains, although this only reached statistical significance in B6 mice (Fig 1B and Table 1). Following access to a moderate fat diet, B6 mice increased caloric intake throughout the 7 days, while the A/J mice only transiently increased caloric intake, returning to baseline after 3 days (Fig 1B). There was no effect of T_a on this ingestive response. Both strains generally exhibited reduced water intake during consumption of the moderate-fat diet (Table 1).

Vo_2, RQ, and Locomotor Activity

We observed no baseline strain differences in the dark- or light-phase normalized Vo_2 (Fig 2C and D and Table 2). As expected, mice housed at thermoneutrality exhibited lower baseline Vo_2 (Fig 2A through D and Table 2). Access to the moderate-fat diet elevated Vo_2 across time for all groups, independent of temperature and circadian phase (Fig 2A through D). We examined the magnitude of increase for absolute and normalized Vo_2 for the treatment period during the

Table 2. Baseline Characteristics for B6 and A/J Mice Housed at 23°C and 30°C

	B6 (23°C)	B6 (30°C)	A/J (23°C)	A/J (30°C)
Absolute Vo_2 (mL/min)				
Light	1.68 ± 0.09	0.89 ± 0.05†	1.52 ± 0.08	0.85 ± 0.05†
Dark	2.24 ± 0.04	1.43 ± 0.07†	1.91 ± 0.10*	1.19 ± 0.09†
Normalized Vo_2 (mL/min/kg$^{0.75}$)				
Light	24.33 ± 0.63	14.34 ± 0.43†	26.03 ± 1.14	16.66 ± 1.30†
Dark	32.39 ± 0.63	22.77 ± 0.47†	32.58 ± 1.12	21.78 ± 1.11†
Respiratory quotient (CO_2/O_2)				
Light	0.849 ± 0.004	0.886 ± 0.008	0.891 ± 0.018	0.872 ± 0.026
Dark	0.934 ± 0.005	0.925 ± 0.001	0.952 ± 0.006	0.923 ± 0.24
Heart rate (bpm)				
Light	587 ± 16	409 ± 12†	597 ± 22	480 ± 17†
Dark	636 ± 7	486 ± 15†	657 ± 5	571 ± 25*
Mean arterial pressure (mm Hg)				
Light	105 ± 2	95 ± 6	101 ± 6	85 ± 4
Dark	119 ± 2	104 ± 3†	117 ± 5	96 ± 5†
Locomotor activity (m)				
Light	50 ± 6	44 ± 3	32 ± 8	30 ± 4
Dark	196 ± 18	244 ± 17	87 ± 12*	91 ± 14*

NOTE. Values are mean ± SEM. See Figs 2, 4, and 5 for n values.
*$P < .05$ *v* B6 mice.
†$P < .05$ *v* $T_a = 23°C$.

light phase (where there were no effects on locomotor activity; Fig 3 and Table 2). The adaptive increase in Vo_2 was not influenced by T_a; therefore, data from both temperatures were pooled for the B6 and A/J mouse strains. There was no significant difference in the magnitude of adaptive thermogenesis between A/J and B6 mice (Fig 4).

Baseline RQ was similar for all groups in both the light and dark cycles (Table 2). Light-phase RQ increased in all groups at day 1, although by day 7 all groups had returned to basal levels (Fig 2F). However, the B6 mice at $T_a = 30°C$ increased light-phase RQ from days 1 to 5, while all other groups increased RQ for only 1 day. Dark-phase RQ increased at day 1 at both temperatures for B6 mice, although only B6 at $T_a = 23°C$ remained different from baseline by day 7 (Fig 2E). Given the substantial increase in total caloric intake, it is likely that the increase in RQ reflects the probability that the mice were in positive energy balance and engaged in lipogenesis.

Light-phase locomotor activity was not different between groups or across time during the experiment (Fig 3). However, at both temperatures, B6 mice had elevated dark-phase baseline locomotor activity compared to A/J mice (Table 2). All groups except B6 mice at $T_a = 23°C$ demonstrated increases in dark-phase locomotor activity on day 1 of fat feeding, although activity returned to baseline levels by day 7 for all groups.

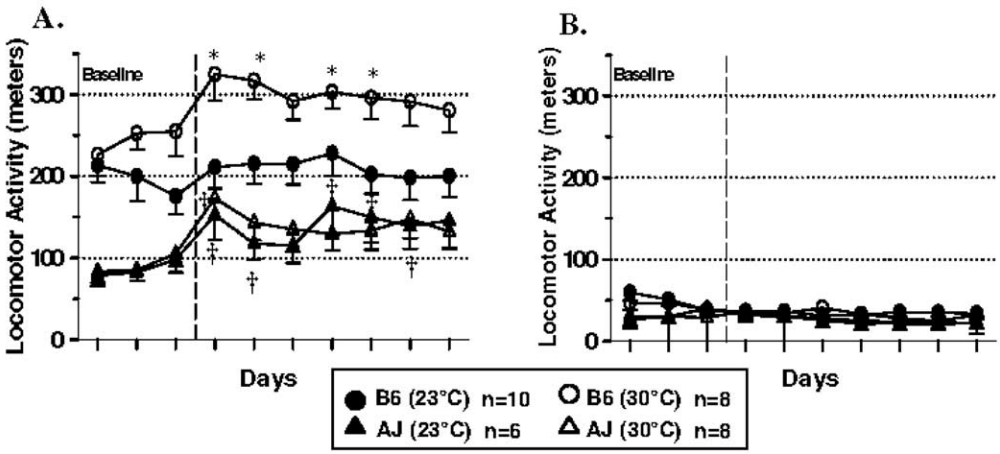

Fig 3. (A) Dark-phase and (B) light-phase locomotor activity in B6 (circles) and A/J (triangles) mice at $T_a = 23°C$ (filled symbols) and $T_a = 30°C$ (open symbols) during 3 baseline days and 7 days of moderate fat diet. Powdered chow (3.3 kcal/g) was provided ad libitum during baseline, while powdered moderate-fat diet (4.41 kcal/g) was provided ad libitum during the 7-day nutritional intervention. *$P < .05$ *v* baseline for B6 mice; †$P < .05$ *v* baseline for A/J mice.

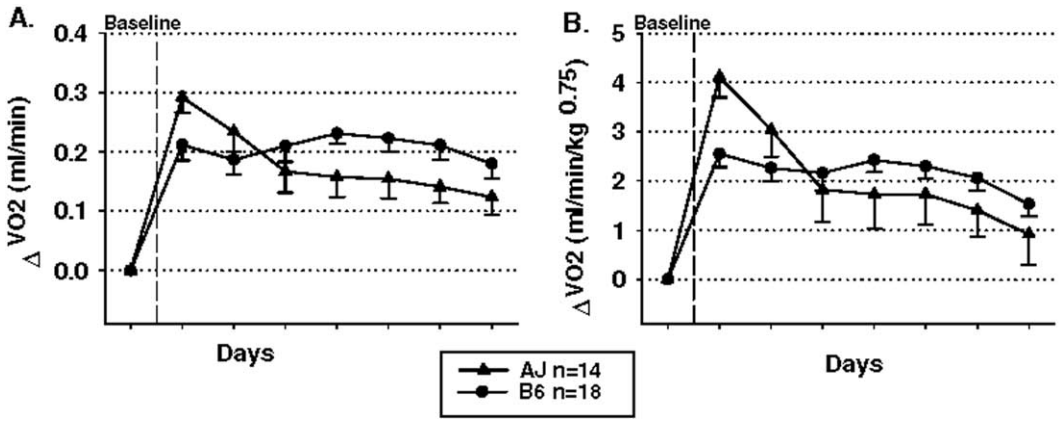

Fig 4. Increase in light-phase absolute and normalized Vo_2 in B6 (circles) and A/J (traingles) mice. Data from both T_a = 23°C and T_a = 30°C were combined in the B6 and A/J mice because the magnitude of increase was not different between temperature within strains.

Heart Rate and Blood Pressure

There were no strain differences in baseline MAP or HR at either T_a (Table 2), with the exception of A/J mice having an elevated dark-phase HR at thermoneutrality compared to B6 mice. As previously observed, mice housed at thermoneutrality exhibit lower MAP (at least 10 mm Hg) and HR (up to 150 bpm).[15,16] Consumption of the moderate-fat diet produced no effect on MAP (data not shown) and modest tachycardia (Fig 5). B6 mice studied at T_a = 23°C exhibited slight and inconsistent tachycardia, while B6 mice studied at T_a = 30°C had elevated HR for all days on the moderate-fat diet during both the dark (Fig 5A) and light phases (Fig 5B and Fig 6). A/J mice had similar responses at both temperatures, although the increases in HR response across time did not reach significance at T_a = 30°C. However, the magnitude of light-phase tachycardia on the first day of moderate-fat feeding was substantially greater for both strains in thermoneutral conditions (Fig 6).

DISCUSSION

We tested the hypothesis that adaptive thermogenesis and cardiovascular responses to consumption of excess calories would be augmented in mice resistant to obesity, and blunted in mice after adaptation to thermoneutrality. The report contains several significant findings. Surprisingly, thermoneutrality did not attenuate the increase in Vo_2 following access to a moderate-fat diet in the 2 strains of mice studied. Although A/J mice exhibited slightly greater initial diet-induced increase in Vo_2 compared to B6 mice, it is unlikely this difference is a major mechanism rendering these mice resistant to diet-induced obesity. Instead, we observed that a clear strain difference in the caloric intake response to moderate fat consumption. A/J mice promptly return to baseline caloric intake within 3 days, while B6 mice remained hyperphagic for the duration of this 7-day study. Unexpectedly, we observed that hyperphagia-induced tachycardia associated with initial con-

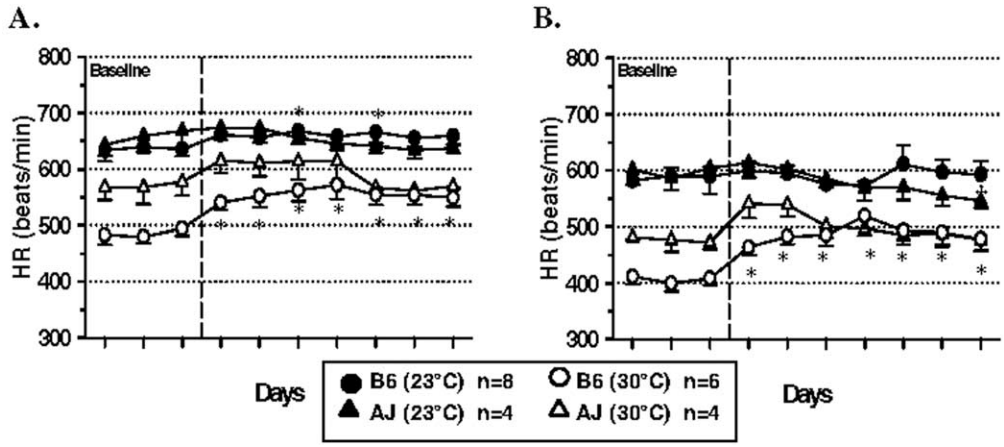

Fig 5. (A) Dark-phase and (B) light-phase HR in B6 (circles) and A/J (triangles) mice at T_a = 23°C (filled symbols) and T_a = 30°C (open symbols) during 3 baseline days and 7 days of moderate fat diet. Powdered chow (3.3 kcal/g) was provided ad libitum during baseline, while powdered moderate-fat diet (4.41 kcal/g) was provided ad libitum during the 7-day nutritional intervention. *$P < .05$ *v* baseline for B6 mice; †$P < .05$ *v* baseline for A/J mice.

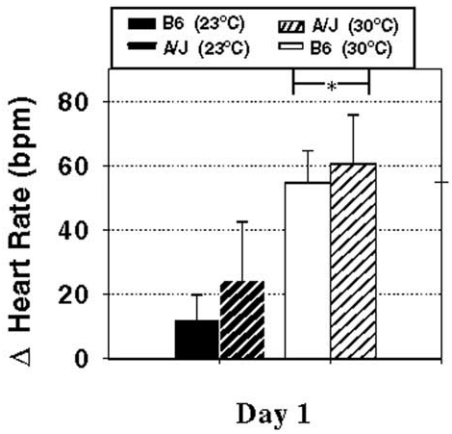

Fig 6. Diet-induced changes in HR in B6 (solid bars, n = 8 at T_a = 23°C and n = 6 at T_a = 30°C) and A/J (hashed bars, n = 4 at T_a = 23°C and T_a = 30°C) mice at T_a = 23°C (filled bars) and T_a = 30°C (open bars) during the light phase. Each bar represents the change in HR on day 1 of moderate-fat diet (4.41 kcal/g) intake compared to the 3-day baseline mean on powdered chow (3.3 kcal/g). *$P < .05$ temperature effect.

sumption of the moderate-fat diet was only evident at thermoneutrality.

Although the magnitude of diet-induced adaptive thermogenesis was not influenced by T_a, baseline V_{O_2} was decreased by about 40% at T_a = 30°C in both strains. The mice were housed at T_a = 30°C for 5 weeks before the nutritional intervention to minimize the potential contribution of BAT to thermogenesis. We did not measure BAT weight in these mice, but it is generally accepted that BAT atrophies and has markedly reduced thermogenic capacity after long-term exposure to thermonuetrality.[24,25] Therefore, it was an unexpected finding that long-term housing of mice in a thermoneutral environment did not attenuate the magnitude of increase in V_{O_2} following access to a moderate-fat diet. Although previous reports have demonstrated that adaptive thermogenesis is impaired at warmer temperatures in rats,[26,27] we are unaware of similar data in mice. Because adaptive thermogenesis appears to be intact at thermoneutrality in mice, we suggest that metabolically active tissues other than BAT can be major sources of diet-induced thermogenesis. Ma and Foster have demonstrated that cafeteria feeding in rats increases tissue-specific V_{O_2} in liver and not BAT.[28] Thus, we speculate that the liver is one major source of adaptive thermogenesis associated with overfeeding. Our findings are consistent with the hypothesis that BAT is not a primary source of diet-induced adaptive thermogenesis in rodents.

The finding that B6 and A/J mice differentially regulate food intake over 1 week of access to a moderate fat chow is interesting, considering previous reports that both strains consume kilocalorie levels similar to a low-fat chow.[9-13] Although caloric intake has reported to be only transiently increased with high-fat feeding in C57 mice,[10] our finding is consistent with another report indicating that B6 mice take more than 2 weeks to regulate caloric intake back to low-fat (4.5% fat) chow levels with ad libitum access to a higher fat diet.[14] One mechanism responsible for the divergent feeding behavior in these mice may be differential leptin signaling or responsiveness. Two weeks on a moderate-fat diet resulted in a greater increase in white adipose tissue leptin mRNA in A/J compared to B6 mice,[10] as well as higher plasma leptin following 4 weeks of access to a high-fat diet.[30] In addition to plasma leptin differences, pro-opiomelanocortin mRNA is increased in A/J, but not B6 mice, although this finding occurred after access to a high-fat diet for 14 weeks.[13] Both B6 and A/J exhibit a preference for a higher fat diet compared to a high-carbohydrate or low-fat chow diet[31]; thus it is not expected that taste preference played a role in the divergent food intakes. An improved understanding of the mechanism responsible for the differential regulation of caloric intake in A/J and B6 mice could provide important information regarding obesity resistance of the A/J mice.

Increased spontaneous activity has been suggested to play a role in obesity resistance in humans.[6,32] Our data are in agreement with previous reports demonstrating that at baseline and following long-term overfeeding, B6 mice are more active than A/J mice.[9,33] We observed significant increases in locomotor activity in both strains of mice when provided access to a moderate fat diet. Interestingly, there was clearly no effect of increased caloric intake on activity in the light phase in either strain. It is not clear if greater difference in activity would develop with continued moderate-fat feeding the might contribute to some strain difference in susceptibility to obesity.

We predicted that overfeeding-induced thermogenesis would be associated with tachycardia, and that this response might be augmented in obese resistant A/J mice. Interestingly, tachycardia of 50 to 60 bpm was only observed in mice studied at thermonuetrality. Mice have a much lower resting HR at thermonuetrality.[15,16,34] Our evidence indicates this is due to both reduced cardiac sympathetic tone and increased cardiac vagal tone[15]; thus it is perhaps not surprising that it is easier to detect tachycardia with overfeeding in mice studied at thermoneutrality. In larger mammals (including humans), overfeeding produces tachycardia that is often associated with both increased sympathetic tone[35,36] and vagal withdrawal.[37-39] While mice are frequently reported to lack vagal control of HR, we have recently shown that this is the case only at standard laboratory temperatures, which represents a cold stress. In mice treated with the β_1-blocker atenolol, HR decreases by about 100 bpm when B6 mice are warmed from T_a = 23°C to T_a = 30°C, indicating a vagally mediated component to the bradycardia at thermoneutrality in mice.[15] Thus, it is possible that the lack of tachycardia observed at standard laboratory temperatures in mice studied at 23°C is explained by lack of vagal tone. We hypothesize that when this mild cold stress is removed, vagal tone is restored, resting HR is lower, and the effects of overfeeding on the cardiovascular system are now evident. Additional studies are required to examine this hypothesis.

In conclusion, this study demonstrates that the thermogenic effect of overfeeding is evident in mice studied at thermoneutrality. During access to a moderate-fat diet, both the obesity-prone B6 and obesity-resistant A/J mice exhibit increases in V_{O_2} regardless of T_a. However, B6 mice displayed hyperphagia throughout the 7-day experiment (compared to only 2 days for the A/J mice). The prompt return to control levels of caloric intake in A/J mice provided a palatable moderate-fat diet, irrespective of ambient temperature, suggests that this is a

primary mechanism rendering this mouse strain resistant to diet-induced obesity. In addition, we conclude that the cardiovascular response to overfeeding is dependent on T_a. These data demonstrate the importance of T_a on mouse physiology, and the need for further investigation of the autonomic regulation at warmer ambient temperatures in mice.

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