Low 24-hour core body temperature as a thrifty metabolic trait driving catch-up fat during weight regain after caloric restriction

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Calonne J, Arsenijevic D, Scerri I, Miles-Chan JL, Montani JP, Dulloo AG. Low 24-hour core body temperature as a thrifty metabolic trait driving catch-up fat during weight regain after caloric restriction. *Am J Physiol Endocrinol Metab* 317: E699 –E709, 2019. First published August 20, 2019; doi:10.1152/ajpendo.00092.2019.—The recovery of body weight after substantial weight loss or growth retardation is often characterized by a disproportionately higher rate of fat mass vs. lean mass recovery, with this phenomenon of “preferential catch-up fat” being contributed by energy conservation (thrifty) metabolism. To test the hypothesis that a low core body temperature (T<sub>c</sub>) constitutes a thrifty metabolic trait underlying the high metabolic efficiency driving catch-up fat, the Anipill system, with telemetry capsules implanted in the peritoneal cavity, was used for continuous monitoring of T<sub>c</sub> for several weeks in a validated rat model of semistarvation-refeeding in which catch-up fat is driven solely by suppressed thermogenesis. In animals housed at 22°C, 24-h T<sub>c</sub> was reduced in response to semistarvation (−0.77°C, P < 0.001) and remained significantly lower than in control animals during the catch-up fat phase of refeeding (−0.27°C on average, P < 0.001), the lower T<sub>c</sub> during refeeding being more pronounced during the light phase than during the dark phase of the 24-h cycle (−0.30°C vs. −0.23°C, P < 0.01) and with no between-group differences in locomotor activity. A lower 24-h T<sub>c</sub> in animals showing catch-up fat was also observed when the housing temperature was raised to 29°C (i.e., at thermoneutrality). The reduced energy cost of homeothermy in response to caloric restriction persists during weight recovery and constitutes a thrifty metabolic trait that contributes to the high metabolic efficiency that underlies the rapid restoration of the body’s fat stores during weight regain, with implications for obesity relapse after therapeutic slimming and the pathophysiology of catch-up growth.

INTRODUCTION

The ability of humans and other mammals to adapt to food scarcity by increasing the efficiency of energy utilization has been well documented in longitudinal studies of experimental starvation and caloric restriction through the demonstration of reduced energy expenditure beyond that explained by losses in body weight and fat-free mass (36, 37). This capacity for energy conservation is viewed as an outcome of regulatory or adaptive processes that, in response to a deficit in energy intake, suppress thermogenesis, hence resulting in a diminished rate of weight loss and a lower energy cost of weight maintenance relative to that predicted by the energy deficit. This suppression of thermogenesis has also been shown to persist during weight regain and is believed to contribute to the disproportionately faster recovery of fat relative to that of lean tissue (5, 11, 21, 28, 34, 35, 56). Indeed, the demonstrations in a rat model of semistarvation-refeeding in which the refed animals are pair-fed with control animals matched for weight at the onset of refeeding have suggested that the energy spared by suppressed thermogenesis is used to enhance specifically the recovery of the body’s fat reserves but not the recovery of lean tissue (19, 20). Such thrifty metabolism for preferential catch-up fat is thought to have evolved for the rapid restoration of the survival capacity conferred by the fat reserves during an ancestral life characterized by periodic food shortage. It is nowadays an important factor that contributes to the relapse of obesity after therapeutic slimming as well as to the disproportionately higher rate of body fat relative to lean tissue deposition commonly observed in adults recovering weight after malnutrition, anorexia nervosa, or cancer-cachexia (22) and in infants and children during catch-up growth after earlier growth perturbations (17).

Although the mechanisms that underlie the thrifty metabolism that drives catch-up fat are not well understood, studies using a rat model of semistarvation-refeeding in which catch-up fat is driven solely by suppressed thermogenesis (13, 19) suggest a potential role for the skeletal muscle rather than brown adipose tissue (BAT) as an important effector site for energy conservation during weight regain. Indeed, although BAT uncoupling protein 1 (UCP1) expression is downregulated during the period of caloric restriction, it is rapidly restored to control levels during early refeeding such that there are no differences in BAT UCP1 between refed and control animals during the phase of catch-up fat (48). By contrast, several lines of evidence suggest that skeletal muscle metabolism is diminished during the catch-up fat phase, including decreased insulin-stimulated glucose utilization (9, 43) and decreased subsarcolemmal mitochondrial mass and oxidative capacity (12). Furthermore, during both phases of caloric restriction and catch-up fat, hindlimb skeletal muscles show features of diminished intracellular availability of 3,5,3′-triiodothyronine (T<sub>3</sub>, the biologically active thyroid hormone), delayed contraction-relaxation kinetics, and increased proportion of slow-twitch at the expense of fast-twitch muscle fibers...
(14) as well as diminished rate of protein turnover (8), which collectively constitute mechanisms that could underlie diminished skeletal muscle thermogenesis during weight loss and weight regain.

Besides these mechanisms of thrifty metabolism in skeletal muscle, other energy conservation mechanisms may also operate. In this context, one possible mechanism of enhanced energy efficiency that has not received much attention is a potential reduction in the metabolic cost of homeothermy, which could be achieved by a modest lowering of core body temperature (Tc). According to Landsberg (39), a lower Tc could be considered a thrifty metabolic trait, conserving energy to better cope with famine but predisposing to fatness. In fact, it has long been known that Tc falls in response to starvation and contributes to the adaptive fall in energy expenditure during weight loss (3, 4, 49). Furthermore, hibernation and the occurrence of spontaneous daily torpor as well as cold- and fasting-induced torpor observed in many rodents are examples of strategies used by mammals to conserve energy by lowering Tc (1, 31, 55).

Here we address, using this rat model of semistarvation-refeeding, the question as to the extent to which a lower Tc, as a thrifty metabolic trait during caloric restriction, persists during refeeding and may thus contribute to the phenomenon of preferential catch-up fat. Using a state-of-the-art approach to assess Tc through the use of abdominally implanted telemetry pills (which allow continuous monitoring of Tc over weeks), we report here that the fall in Tc in response to caloric restriction persists during the catch-up fat phase of refeeding conducted at typical laboratory room temperature (22°C) or at thermoneutrality (29°C).

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats (Elevage Janvier, Le Genest Saint Isle, France), 6 wk old, were acclimatized to room and cage environments for at least 5 days before the start of each experiment. They were caged singly in a controlled room (22 ± 1°C) with a 12:12-h light-dark cycle and maintained on a commercial pelleted chow diet (Provimi Kliba, Switzerland) consisting, by energy, of 24% protein, 66% carbohydrate, and 10% fat and had free access to tap water. Animals were maintained in accordance with the regulations and guidelines of the Department of Medicine, University of Fribourg, for the care and use of laboratory animals; all experimental procedures were performed under conditions approved by the Ethical Committee of the State of Fribourg Veterinary Office.

Experimental design. Two separate experiments were performed according to designs depicted in Fig. 1. The experiments in the rat were conducted in the age range of 7–12 wk, i.e., during a period when spontaneous growth is characterized by a linear rate of weight gain with ad libitum daily food intake relatively constant (Fig. 1A). This pattern of food intake in spontaneously growing Sprague-Dawley rats under conditions in our laboratory has been reported previously (57) and is also observed in the present study (Fig. 1B).

In experiment I (Fig. 1, B and C), after a housing acclimatization period of 1 wk followed by another week of postsurgical recovery, two groups of rats (n = 10) housed at 22°C were either fed ad libitum on the chow diet or food restricted for 2 wk at 50% of the chow intake of ad libitum-fed rats; this level of food restriction has repeatedly been shown to result in growth arrest, i.e., without significant gain or loss in body weight and lean mass but with a 50% reduction in body fat relative to the onset of semistarvation (13, 19, 57). At the end of this semistarvation (SS) period corresponding to day 0 of refeeding (Fig. 1B), half of the rats in each group were killed for the analysis of initial body composition before the refeeding phase. The remaining ad libitum-fed rats (n = 5), referred to as age-matched (AM) control rats, continued to be fed ad libitum, whereas the remaining semistarved rats (n = 5) were refed the chow diet and referred to as the semistarved-refed (SS/RF) group; these SS/RF animals were refed at a level approximately equal in metabolizable energy (ME) content to the spontaneous food intake of a third group of rats (n = 5) matched for weight relative to the SS/RF group at the onset of refeeding and referred to as the weight-matched (WM) control group; another group of WM control rats of similar mean body weight (n = 5) were killed for the analysis of body composition before the refeeding period.

During the phase of refeeding (days 0–16; Fig. 1B), the SS/RF group therefore consumed, on a day-to-day basis, the same amount of food energy as the WM control group fed ad libitum. Under these conditions, previous work in our laboratory has repeatedly demonstrated that SS/RF animals showed a similar gain in lean mass but an about two- to threefold increase in body fat gain compared with control rats over a period of 2–3 wk, because of 10–13% lower energy expenditure resulting from suppressed thermogenesis (8, 13, 19, 22–24, 42). These fundamental aspects of this rat model in which catch-up fat results from a high efficiency of fat deposition (relative to both control groups) are confirmed here: 1) The semistarvation resulted in growth arrest, with body weights of the food-restricted rats (between 235 and 240 g) only slightly and nonsignificantly reduced relative to their weights at the onset of the food restriction period (Fig. 1B). 2) Comparison of body composition at the end of the 2-wk period of growth arrest due to semistarvation shows that the SS animals have significantly lower body fat (−50%, P < 0.01) than WM control animals, but they did not differ in lean mass (Fig. 1B, right, time point 0). 3) During the refeeding period, while the gain in lean mass was similar in all groups (Fig. 1B), the refeed (SS/RF) animals showed a twofold increase in body fat relative to the control groups, this preferential catch-up fat (relative to control) being explained by a high energetic efficiency for fat deposition (Table 1).

In experiment II (Fig. 1D), after 1 wk of housing acclimatization and 1 wk of postsurgical recovery followed by 2 wk of semistarvation, the semistarved animals (n = 7–8) were refed isocalorically to WM control animals for a period of 21 days. During the different periods in this experiment, the laboratory room temperature was maintained either at 22°C or at 29°C as depicted in Fig. 1D.

In both experiments I and II, core body temperature (Tc, recording) was measured continuously while 24-h locomotor activity monitoring was performed at two different time points indicated in Fig. 1, C and D, for experiments I and II, respectively.

Surgery and continuous core body temperature monitoring. The DSI Anipill system (BodyCap, Caen, France) was used for continuous monitoring of Tc at 5-min intervals while 24-h locomotor activity monitoring was performed at two different time points indicated in Fig. 1, C and D, for experiments I and II, respectively.

Ex vivo capsule calibration. All telemetry capsules used in this study were validated for accuracy against mercury (Hg) thermometers (range 34–40°C; VWR, Dietikon, Switzerland) before implantation in the animals as well as after their removal from the animals at the end of the experiment; the calibration procedures have been described in detail previously (44). Briefly, capsules were compared against the Hg thermometers, all placed in a digital water bath (2.6 liters; VWR, Dietikon, Switzerland), and a stepwise increase in temperature was performed from 35 to 40°C with a period of stabilization of 5–8 min
Fig. 1. Design of experiments. A: the growth profile and daily food intake of male Sprague-Dawley rats (mean ± SE; n = 10) maintained on standard chow diet ad libitum between age 3 and 25 wk under conditions of our laboratory (57); the dotted rectangle encloses the age range (7–11 wk) and growth period pertaining to our studies of food restriction and refeeding and during which the rats show rapid increases in body weight (P < 0.001). Within this age range of 7–11 wk, food intake was not significantly different across time, such that providing half the chow daily corresponds to 50% reduction of ad libitum food intake throughout this period [reproduced from Yepuri et al. (57) with permission]. B: the growth profile and food intake (g chow/day) of the 3 groups of animals (n = 5/group) in experiment I during the phases of acclimatization, semistarvation, and refeeding (days 0–16). C and D: for experiments I and II, respectively, the various periods (acclimatization, semistarvation, and refeeding), time points for capsule calibration, surgery for capsule implantation, and the periods of core body temperature (T_c) recording and locomotor activity (A) monitoring. AM, age matched; d, day, SS/RF, semistarved and then refed; WM, weight matched.
after each 1°C increase in temperature. Recordings were taken during the stabilization period, every minute for 8 min. All investigations (including calibrations) were carried out by the same investigator.

**Locomotor activity.** Locomotor activity was recorded continuously for two consecutive days at two different time points during each of the experiments with an in-house-built activity monitoring system that utilizes infrared diode system and calculation of center of gravity. Briefly, for monitoring locomotor activity, an animal cage with transparent walls and housing an individual rat was placed inside of a metallic rectangular frame presenting 24 infrared light-emitting diodes (LEDs) at 80-mm intervals. On the opposite side of each axis, 24 light-sensitive phototransistors detected whether the infrared light transmitted signal was interrupted by the animal crossing its path. All diodes were scanned sequentially twice a second, allowing us to know the position of the animal twice a second. From the interrupted beams, a global center of gravity was calculated. The displacement of this center of gravity over time would give the path traveled by the animal during the experiment.

**Body composition analysis.** After the animals were killed, the whole carcasses were dried to a constant weight in an oven maintained at 70°C. They were subsequently homogenized, and aliquots were taken during refeeding by the comparison of body energy deposition. Total body energy content and Δbody energy can be calculated from a general formula relating the total energy value of the carcass, energy derived from fat, and energy derived from protein (13). The efficiency of deposition of body energy, fat, or protein during refeeding is calculated as the gain in total body energy, fat energy, or protein energy as a percentage of the ME intake.

**Data analysis and statistics.** All data are presented as means ± SE. One-way analysis of variance (ANOVA) followed by post hoc pairwise comparisons using Scheffé’s test or unpaired t tests was used to assess the effects of semistarvation and refeeding on the Tc of rats and also on the locomotor activity (using the significance level of P < 0.05). The statistical treatment of data was performed with the computer software Statistix, version 8.0 (Analytical Software, St. Paul, MN).

RESULTS

**Ex vivo capsule calibration.** The results of capsule calibration against Hg thermometers before implantation of the capsule in the animal and after its removal at the end of experiments I and II indicated that the values of mean bias for capsule temperature were lower than those of Hg thermometer readings by −0.54°C on average (range −0.40°C to −0.68°C). However, when examined across time, the mean bias value for each capsule showed little or no deviation from the initial value, suggesting no drift in capsule temperature readout over time. The values of Tc reported in the results for experiments I and II below have been corrected for deviations from the average Hg thermometer readings before capsule implantation and after removal from the animal across a given experiment.

**Experiment I: Tc during caloric restriction and subsequent refeeding.** The 24-h Tc profiles for the three groups of rats during the periods of acclimatization, semistarvation, and refeeding are shown in Fig. 2. In the acclimatization period (Fig. 2A) all groups showed similar Tc profiles across the 24-h period, with Tc being higher during the dark phase (1800–0600) than during the light phase (0600–1800) by 0.3–0.5°C. At the end of the 2-wk period of caloric restriction (Fig. 2B), however, the semistarved group showed lower Tc relative to both AM and WM control groups, particularly in the second
half of the dark phase extending into the first half of the light phase, namely, by >0.5°C between 0000 and 1200. Within this same time period of midnight to midday, Tc was also found to be lower in the refed group than in the two control groups, whether after days 2–3, days 6–7, or days 10–11 of refeeding (Fig. 2, C, D, and E, respectively). When integrated over the entire 24-h period, the values of Tc were not different between the three groups in the acclimatization period (Fig. 2A), were lower by ~0.4°C in the semistarved group than in the control groups (Fig. 2B), and also remained lower in the refed group than in the control groups by ~0.4°C (P < 0.001) on days 2–3 (Fig. 2C) and by ~0.2–0.3°C (P < 0.05) on days 6–7 as well as on days 10–11 of refeeding (Fig. 2, D and E, respectively). During all phases and time points of measurements, no significant differences in Tc were observed between the two control groups (AM and WM), whether examined across the dark and light periods or integrated over 24 h.

The data on locomotor activity assessed over 24 h at the end of semistarvation and on days 6–7 of refeeding are shown in Fig. 3. The locomotor activity profile over 24 h at the end of the caloric restriction period (Fig. 3A) indicates that the semistarved group showed lower locomotor activity than in the WM control animals in the later part of the dark phase (0000–0600; P < 0.01), resulting in the integrated 24-h value being lower by 30% (P = 0.06). Assessment of locomotor activity during days 6–7 of refeeding, however, showed no significant differences in refed animals compared with the control groups, whether examining the dark or light phases or the integrated 24-h values (Fig. 3B). Overall, although a lower locomotor activity can be associated with a lower Tc during the period of caloric restriction, the persistently lower Tc during refeeding occurred without a lower locomotor activity in the refed animals compared with control animals.

**Experiment II: Impact of thermoneutrality on Tc in response to caloric restriction and refeeding.** To investigate whether the lower Tc during refeeding persists under conditions of thermoneutrality, we repeated the study above in the rat model of semistarvation and refeeding with the laboratory temperature maintained at 22°C, except for 24 h in each period when the ambient temperature was maintained at 29°C, namely, at the end of the acclimatization period, during days 6–7 and 11–12 of the semistarvation period, and during days 6–7, 13–14, and 20–21 of the refeeding period. During the latter periods, food intake in the control animals was lower at 29°C than at 22°C (~22 vs. 26 g/day), and the refed animals were provided with the same amount of chow as the control animals both at 22°C (26 g/day) and at 29°C (22 g/day), such that the food intakes of the refed animals were the same as control animals throughout the refeeding period, including during periods at 29°C. The results for Tc, shown in Fig. 4A, indicate that independently of the ambient temperature (22°C or 29°C), the 24-h Tc was significantly lower in the semistarved group than in the control animals, namely, by ~0.4°C and ~0.35°C at 22°C and 29°C, respectively, on days 6–7 of semistarvation and by ~0.65°C and ~0.5°C at 22°C and 29°C, respectively, during days 11–12 of semistarvation. During the course of refeeding, Tc remained
lower in the refed than control animals independently of the ambient temperature, namely, by approximately $-0.3°C$ between days 4 and 20 of refeeding, albeit with the difference in $T_c$ becoming less marked on days 21–22 conducted at thermalneutrality; the between-group comparisons for 24-h $T_c$, together with statistical significance of differences, are also shown separately at 22°C and at 29°C (Fig. 4, B and C). No significant differences in 24-h locomotor activity were observed between refed and control animals when assessed at 22°C or at 29°C on days 12–14 as well as on days 19–21 of refeeding (data not shown); this contrasts with the significantly lower values of $T_c$ in the refed animals than in control animals over these same time periods.

**DISCUSSION**

It has long been recognized that $T_c$ falls in response to caloric restriction and that this reduction in the cost of homeothermy is part of the adaptive mechanisms contributing to energy conservation during food scarcity. The studies reported here, in a rat model of catch-up fat driven by suppressed thermogenesis (13, 19), suggest that diminished $T_c$ in response to caloric restriction persists during weight recovery upon refeeding, and such diminished cost of homeothermy is a component of the energy conservation mechanisms directed at accelerating the restoration of the body’s fat reserves during weight regain.

**Contribution of lower $T_c$ to energy conservation driving catch-up fat.** Previous work in our laboratory (13, 19, 20) and in others (11, 12, 26), using this rat model of semistarvation-refeeding, has consistently shown that the high efficiency of catch-up fat lasts for several weeks. Our study here demonstrates diminished $T_c$ during the catch-up fat phase of refeeding in a design where 1) the accuracy of capsule temperature readout and potential drift across time were validated by performing ex vivo calibration of each capsule before and after each experiment and also, importantly, 2) under conditions in

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Fig. 4. **A:** core body temperature ($T_c$) of rats that were semistarved (SS) and subsequently refed (RF) (orange), and their weight-matched controls (black), with the ambient temperature maintained at 22°C or 29°C. D, day. B and C: data are presented as 24-h $T_c$ at 22°C (B) and 29°C (C) for 24-h $T_c$. In B and C, significant between-group differences at each time point are indicated as follows: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. n = 7 or 8/group.
which refed animals were compared with time control animals that were of either the same age or the same weight at the onset of refeeding.

In past studies from our laboratory, we were able to quantify the energy conserved for preferential catch-up fat in this rat model as representing ~12% of total energy expenditure relative to control rats matched for weight and protein mass at the onset of refeeding (i.e., the WM control rats) (13, 19, 23, 24, 42). These findings, based upon estimating energy expenditure by energy balance and body composition changes, have been confirmed by other laboratories in studies of energy balance coupled with 24-h assessment of energy expenditure by indirect calorimetry (11, 26). Indeed, using the same experimental design, Crescenzo et al. (11) reported that compared with WM control rats isocalorically refed rats showed an elevated energetic efficiency and body fat gain over both week 1 and week 2 of refeeding, as well as a lower 24-h energy expenditure (assessed by indirect calorimetry) at the end of both week 1 and week 2 of refeeding by ~7% and ~11%, respectively. This pattern of suppressed thermogenesis after refeeding has also been reported in mature but growing rats allowed ad libitum refeeding after 2 wk of 60% caloric restriction (26). In the latter study, a very mild and transient hyperphagia during refeeding was shown to be accompanied by a sustained suppression of daily energy expenditure (~11% and ~6% in Sprague-Dawley and Long-Evans rats, respectively) that remained evident more than a week after refeeding (26).

A number of factors that could contribute to the difference in energetics between the refed animals and the 2-wk-younger WM control animals (namely, age, meal pattern, and size of organs) have been evaluated previously and were shown to have little or no impact on the difference in energy expenditure between the two groups (19, 20, 22–24). Indeed, with a similar age difference of 2 wk between the refed and WM control animals, the two control groups (AM vs. WM controls) showed no significant differences in their rate of growth (i.e., similar gain in fat mass and lean mass; Fig. 1B, Table 1) and in the efficiency of energy, fat, and protein deposition (Table 1). These findings when comparing AM and WM control animals within the 7–11 wk age range are in line with our previous studies that also did not find significant differences between these two controls differing by 2 wk of age in their fasting plasma glucose and insulin concentrations or in their glucose and insulin response curves to a glucose load (13). The lack of differences in metabolism between the two control groups, within the design of our study, can now be extended to their 24-h profile of Tc, which was not different between the WM and AM control animals when measured at various time points throughout the 4-wk experiment. Consequently, the lower Tc in the refed groups relative to these two control groups suggests that the lower cost of homeothermy persisting concomitantly with the elevated efficiency of fat deposition during refeeding represents an inherent thrifty metabolism that contributes to the restoration of depleted fat reserves. In light of the estimation by Dubois (16) that a change of 1°C in Tc represents 10–13% of energy expenditure at rest, our findings here that the 24-h Tc is lower by 0.25–0.3°C on average in the refed group than in WM control animals would suggest that 25–30% of the lower energy expenditure driving the preferential catch-up fat phenomenon could be explained by a lower cost of homeothermy.

**Tc and locomotor activity.** In the rat, diminished physical activity and/or Tc has often been reported to occur in association with the diminished energy expenditure in response to starvation or prolonged (weeks) caloric restriction (2, 18, 28, 41). It should be emphasized, however, that the energy expenditure associated with physical activity not only comprises the energy cost of work performed in the environment together with energy lost as heat due to the mechanical inefficiency in performing work but also includes the energy spent on a whole array of metabolic events that may be associated with or triggered by movement (18). Such movement-associated thermogenesis may overlap with movement-associated anticipatory increase in heat production (28, 46), oral-sensory stimulation of metabolic rate associated with the search for food and with actual feeding (27, 28), increased heat production for thermoregulatory needs (7, 33), and isometric thermogenesis associated with muscle tension, such as during spontaneous “fidgeting-like” or grooming activities (33, 45, 46). These studies suggest that in laboratory rodents the actual energy cost of performing work per se is trivial compared with their 24-h energy expenditure whereas the movement-associated thermogenesis is an important component of nonresting energy expenditure that contributes to adaptive thermogenesis in response to cold or to caloric restriction. In our study here, although both locomotor activity and Tc were found to be diminished during caloric restriction, only a lower Tc persisted during the refeeding phase, with no significant differences observed between locomotor activity in refed compared with control animals. However, the possibility of a link between lower Tc and diminished movement-associated thermogenesis during the phase of catch-up fat cannot be disregarded.

**Tc and sympathetic control of BAT thermogenesis: issue of thermoneutrality.** As the animals in our laboratory are housed at 22°C, which is well below the zone of thermoneutrality for the rat, the question arises as to whether the adaptive suppression of thermogenesis and diminished Tc during caloric restriction and refeeding may reside in diminished nonshivering thermoregulatory thermogenesis, which in the rat is well known to be primarily mediated by the activity of the sympathetic nervous system in BAT (29, 40). However, under conditions of thermoneutrality, when sympathetic control of BAT thermogenesis is known to be rapidly suppressed (10, 32, 40), we still observed the drop in daily Tc both during caloric restriction and persisting during subsequent refeeding. This is evidenced by our data indicating that a shift in the ambient temperature from 22°C to 29°C had little or no impact on the diminished Tc at several time points during semistarvation and refeeding. In fact, an adaptive reduction in thermogenesis has been reported in studies of prolonged caloric restriction in rats housed in cool (15°C) or thermoneutral (30°C) conditions (38). It has also been reported during refeeding at 22°C, at thermoneutrality (29°C), or in the cold (6°C) whereby despite pair-feeding with the respective control animals the refed animals still showed greater gain in body fat, due to 10–12% lower energy expenditure than the control animals at each of the three environmental temperatures (23). Taken together, these studies suggest that suppression of the sympathetic-BAT axis is not a critical component of the lower Tc and adaptive suppression of thermogenesis during caloric restriction and the subsequent phase of catch-up fat during refeeding.
Table 2. Summary of previous and present findings in rat model of semistarvation-refeeding

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Comparisons are made between semistarved (SS) rats and their controls (CSS) at the end of 10–14 days of semistarvation and between refeed rats and their controls (CRF) after 7–10 days of controlled refeeding, with both refeed and control rats consuming the same amount of food and refeed rats showing increased efficiency of body fat (but not lean mass) deposition relative to control rats. T₃, 3,5,3’-triiodothyronine; T₄, thyroxine; UCP1, uncoupling protein 1; ↑, increase; ↓, decrease; ≈, no significant difference; —, not measured.

**Set point of the thermoregulatory system.** The possibility therefore remains that suppressed thermogenesis in other organs/tissues may contribute to the accompanying lowering of Tₖ, in particular in the skeletal muscle, for which there is evidence for energy conservation occurring during starvation (41) or during prolonged caloric restriction and persisting during refeeding to contribute to catch-up fat (12, 14). The underlying mechanisms that have so far been implicated are summarized in Table 2 and seem to be associated with a state of skeletal muscle hypothyroidism (8, 14). However, as previously argued (18), “a steady state decrease in total heat production cannot be established without a shift towards lower temperatures of the apparent set point of the thermoregulatory system; otherwise, this feedback system would respond by a stimulation of the effectors of regulatory heat production to counteract the tendency of the body temperature to decrease as a result of the lower heat production, this compensating for the increase in energy efficiency.” Support for this contention can be derived from two rat models with a high metabolic efficiency, ventromedial hypothalamus-lesioned animals and the genetically obese fa/fa rats (6), in which a centrally mediated inhibition of nonshivering thermogenesis has been demonstrated (47, 50, 51). Finally, one may argue that a reduction in Tₖ may also be contributed to by an increase in heat loss. However, such an increase can only be acute and transient and is unlikely to explain the underlying high metabolic efficiency since a steady-state increase in heat loss cannot be sustained without a shift toward higher temperatures of the apparent set point of the thermoregulatory system.

**Perspectives.** The combined effect of increased metabolic efficiency and lower cost of homeothermy is likely to be polyhormonal, since a role for glucocorticoid (24) and thyroid hormones (8, 14, 42) has been implicated in the suppressed thermogenesis driving catch-up fat (summarized in Table 2) and may involve changes in the central regulation of Tₖ. In other words, in addition to peripheral cross talks between the adipose tissue stores and skeletal muscle thermogenesis, one may entertain the possibility of a feedback loop between a deficit in the adipose tissue fat reserves and central control of thermogenesis operating through a shift toward lower temperatures of the apparent set point of the thermoregulatory system. In this context, the fall in leptin that signals lower adipose fat stores (1) in response to starvation or caloric restriction has often been implicated in the diminished locomotor activity, energy expenditure, and Tₖ that characterize daily torpor in some birds and small mammals (15). However, studies in mice with leptin deficiency as well as in leptin receptor-deficient mice have demonstrated that torpor is induced by both leptin-dependent and leptin-independent mechanisms (31) and that leptin is not required for compensatory reduction in energy expenditure accompanying weight loss (30, 31, 52). Furthermore, although explanations and concepts built around torpor-associated reduction in Tₖ may apply to our studies here in the rat showing lower Tₖ during the semistarvation period, they are unlikely to provide an explanation for the persistently lower Tₖ during the phase of catch-up fat for two main reasons. First, although torpor is a state characterized by reductions in Tₖ, energy expenditure, and physical activity, the suppressed thermogenesis driving catch-up fat is associated with persistently lower Tₖ but without a reduction in locomotor activity, thereby casting doubt upon the mechanisms driving the high efficiency of catch-up fat as being torporlike. Second, although leptin is markedly lower than control animals during semistarvation, it is rapidly restored within a few days of refeeding and is subsequently higher than in control animals during most of the phase of catch-up fat driven by suppressed thermogenesis (42). In other words, the lower Tₖ that persists during the 2–3 wk of refeeding cannot be explained by low concentrations of circulating leptin. Overall therefore, the lower Tₖ persisting during the catch-up fat may be part of the complex coordination of rapid recovery of the fat reserves that includes leptin-independent signal(s) from adipose tissue whose actions would lead to
slowdown of energy metabolism in peripheral organs, as evidenced in skeletal muscle (8, 12, 14), as well as centrally (e.g., in the hypothalamus) to lower the set point of the thermoregulatory system. The nature of these adipostat(s) is unknown and remains a challenge for future research on the mechanisms of thrifty metabolism driving catch-up fat, with implications for advances for the pathophysiology of catch-up growth and the ease of obesity relapse after therapeutic slimming.

Concluding remarks. Using a state-of-the-art approach to assess Tc through the use of abdominally implanted telemetry pills (which allow continuous monitoring of Tc over weeks), we report here that the fall in Tc in response to caloric restriction persists during the catch-up fat phase of refeeding conducted at typical laboratory room temperature (22°C) or at thermoneutrality (29°C). The reduced energy cost of homeothermy persisting during the dynamic phase of weight recovery could constitute a thrifty metabolic trait that contributes to the high metabolic efficiency underlying the rapid restoration of the body’s fat stores.

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DISCLOSURES
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AUTHOR CONTRIBUTIONS

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