Regular exercise attenuates the metabolic drive to regain weight after long-term weight loss

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MacLean PS, Higgins JA, Wyatt HR, Melanson EL, Johnson GC, Jackman MR, Giles ED, Brown IE, Hill JO. Regular exercise attenuates the metabolic drive to regain weight after long-term weight loss. Am J Physiol Regul Integr Comp Physiol 297: R793–R802, 2009. First published July 8, 2009; doi:10.1152/ajpregu.00192.2009.—Weight loss is accompanied by several metabolic adaptations that work together to promote rapid, efficient regain. We employed a rodent model of regain to examine the effects of a regular bout of treadmill exercise on these adaptations. Obesity was induced in obesity-prone rats with 16 wk of high-fat feeding and limited physical activity. Obese rats were then weight reduced (~14% of body wt) with a calorie-restricted, low-fat diet and maintained at that reduced weight for 8 wk by providing limited provisions of the diet with (EX) or without (SED) a daily bout of treadmill exercise (15 m/min, 30 min/day, 6 days/wk). Weight regain, energy balance, fuel utilization, adipocyte cellularity, and humoral signals of adiposity were monitored during eight subsequent weeks of ad libitum feeding while the rats maintained their respective regimens of physical activity. Regular exercise decreased the rate of regain early in relapse and lowered the defended body weight. During weight maintenance, regular exercise reduced the biological drive to eat so that it came closer to matching the suppressed level of energy expenditure. The diurnal extremes in fuel preference observed in weight-reduced rats were blunted, since exercise promoted the oxidation of fat during periods of feeding (dark cycle) and promoted the oxidation of carbohydrate (CHO) later in the day during periods of deprivation (light cycle). At the end of relapse, exercise reestablished the homeostatic steady state between intake and expenditure to defend a lower body weight. Compared with SED rats, relapsed EX rats exhibited a reduced turnover of energy, a lower 24-h oxidation of CHO, fewer adipocytes in abdominal fat pads, and peripheral signals that overestimated their adiposity. These observations indicate that regimented exercise altered several metabolic adaptations to weight reduction in a manner that would coordinate the propensity to regain lost weight.

fat oxidation; energy balance; indirect calorimetry; postobese; adipocyte cellularity

WEIGHT REGAIN AFTER WEIGHT LOSS has been repeatedly shown in both obese animals (3, 4, 6, 9, 21–23, 25, 26, 30) and humans (14, 18, 32, 42, 43). A meta-analysis of a large number of U.S. weight loss studies summarized the propensity to regain after a wide variety of weight loss programs (1). Not only does lost weight tend to return, but the rate of return is highest immediately after the cessation of the programmed weight loss program. Over 35% of the lost weight returns in the first year, and the majority is gained back within five years. Most people view their weight loss program as a transient change in their lifestyle and dietary habits or have difficulty in sustaining the changes that they have made to lose the weight (7, 11).

The proposed reasons for the high rate of weight regain are many (11), but there is substantial evidence of an important role for metabolic adaptations that occur in response to weight loss (10, 13). The reductions in leptin and insulin (21, 23–25), in combination with a number of other neural, nutrient, and endocrine signals, convey an “energy deficit” signal to energy balance control centers within the brain. The result is an increased drive to eat (8, 15, 21, 23, 25) and a suppressed energy expenditure (9, 14, 25–27, 33, 35, 44). To maintain the reduced weight, food intake must be proactively limited to the level that expenditure is suppressed. This large energy gap between appetite and expenditure does not dissipate and may even become more profound with time in weight maintenance (26). Peripherally, the increase in insulin sensitivity and reversal of metabolic inflexibility primes tissues to utilize and store the impending caloric excess in an energetically efficient manner, in part because the ability to regulate fat oxidation is restored (2, 15, 38, 41). Additionally, studies in both humans and animals suggest that weight loss can lead to an increase in the number of adipocytes, which could facilitate the repletion and expansion of adipose tissue depots (15, 24, 25). Taken together, these observations provide evidence that the metabolic adaptations to weight reduction not only make it very difficult to sustain the necessary level of calorie restriction, but they also facilitate rapid, efficient weight regain when the inevitable bout of overfeeding occurs.

In light of this metabolic response, it is not surprising that successful weight loss maintenance is a challenging prospect. Ninety percent of those who are successful, as reported from the National Weight Control Registry, include regular exercise as part of their weight maintenance program (20). Poor adherence to exercise prescription, however, has made it difficult to show in randomized, controlled trials that regular exercise is an effective strategy for weight regain prevention (5). Regardless, studies in both animals and humans provide evidence that being more physically active results in less regain (16, 17, 21). The mechanisms that underlie this beneficial effect of physical activity are not clearly understood, but there is evidence to suggest that physical activity counters the biological adaptations to weight loss that facilitate weight regain (21).

In the present study, we employed a well-established rodent model of weight regain to examine the impact of a regular bout of aerobic, treadmill exercise on the homeostatic system that controls body weight. Our approach with this analysis was to provide an integrative picture of how regular endurance exercise affects energy balance, fuel utilization, lipid accretion, and peripheral adiposity signals, all of which are key components...
of the homeostatic system controlling body weight. We hypothesized that several aspects of this system would be coordinately altered in a manner that would facilitate maintenance of the weight-reduced state. Our observations indicate that, in male rats, regular exercise abrogates much of the biological drive to overeat that initiates the relapse to obesity and alters peripheral fuel metabolism and adipocyte cellularity in a manner that would reduce the rate and energetic efficiency of weight regain.

METHODS

Experimental paradigm of weight regain. Male Wistar rats (125–150 g) were purchased from Charles River Laboratories (Charles River Laboratories, Wilmington, MA) and individually housed for the duration of the study in the University of Colorado Denver Center for Comparative Medicine and the Center for Human Nutrition Satellite Facility (22–24°C; 12:12-h light-dark cycle) with free access to water. All procedures were approved by the University of Colorado Denver Institutional Animal Care and Use Committee.

Obesity-prone and obesity-resistant rats were identified by their weight gain response to a high-fat diet (HF, 46% kcal fat, RD no. 12344; Research Diets, New Brunswick, NJ) as previously described (26, 27). These rats were then matured in an obesogenic environment (with free access to the HF diet; individually housed in cages that limit physical activity) for 16 wk to yield obese and lean rats. Twenty-one obese rats were then placed on an energy-restricted low-fat diet (LF, 13% kcal fat, RD no. 11724; Research Diets) for 2 wk, equivalent to ~55% of the calories eaten ad libitum by obese rats to yield a 10–15% reduction in their body weight. The remaining obese and lean rats were switched to ad libitum access of the LF diet for the remainder of the study.

The weight-reduced rats were stratified according to weight and weight loss, and then divided into sedentary (SED) and exercise (EX) groups for the duration of the study. For eight subsequent weeks, the reduced weight was maintained by providing a limited provision of the LF diet at the beginning of each dark cycle (3:00 P.M.), with (EX) or without (SED) a bout of treadmills exercise occurring within the first 3 h of the dark cycle. The relapse to obesity in SED and EX rats was followed for eight subsequent weeks of ad libitum feeding on the LF diet, while their respective daily regimens of inactivity or daily treadmill exercise continued.

Treadmill exercise. At the start of the 8 wk of weight maintenance, EX rats were acclimated to 15 m/min for 30 min/day on 6 days/wk. Two Exer-6M Treadmill (Columbus Instruments), each with three individual lanes, were used for the training regimen. This was accomplished by ramping up the speed from 9 to 15 m/min during a 5-min bout over a 1-wk period, and then ramping up the time from 5 to 30 min over a 2-wk period. Rats were motivated to complete their daily training by using one or more of the following stimuli: 1) positioning food pellets just out of reach or dangling a novel play item at the head of the treadmill lane; 2) shock from an electric grid at the rear of the treadmill (10 volts, 0.5 amps, 0.75 Hz); 3) application of a bristle brush to the feet on the rear grid; and/or 4) intermittent air puffs to the hindquarters. The type and combination of motivation used varied within the same rat and between rats, depending on the response to the motivation. One rat that did not respond to any motivational tool refused to perform any treadmill exercise. This rat was removed from the study. The best technique on a given day for each individual rat was chosen to complete their training session. Rats were scored on a graded scale by the technician for their performance (1 = poor; 10 = outstanding), based on the amount of oversight and encouragement required to ensure compliance. This regimen of exercise continued to the end of the study in EX rats, which included both the weight-loss maintenance and relapse phases of the protocol.
RESULTS

Exercise attenuates weight regain after weight loss. Regular exercise attenuated the rate of weight regain early in the relapse period and reduced the defended body weight (Fig. 1A). The percent of lost weight regained was substantially reduced (120 ± 8 vs. 77 ± 7%, P < 0.05) with regular exercise after the 8 wk of relapse (Fig. 1B). Regular exercise had no impact on body composition during the weight maintenance phase of the study (data not shown), and the attenuated weight gain in the EX rats during relapse was fat mass (Table 1). EX rats exhibited a reduction in tissue weights of the liver, RP, and mesenteric fat pads compared with SED rats at the end of relapse. In addition, relapsed EX rats had fewer adipocytes than relapsed SED rats when cellularity characteristics were assessed in the RP pads (Fig. 1C).

Energy balance during weight regain. Energy balance data are shown in Fig. 2. Energy intake (EI) was significantly lower in weight-reduced rats than in obese ad libitum-fed controls (Fig. 2A), reflecting their calorie-restricted diet regimen. When this restriction was ended, ad libitum intake increased dramatically in SED rats during the first few days of relapse and remained elevated throughout the remainder of the study. Regular exercise prevented this hyperphagia during the early stages of relapse. EI in EX rats was significantly lower than in SED rats throughout most of relapse. SED rats ate more food than obese controls during relapse (P < 0.05), whereas EX rats ate less than obese controls over that time (P < 0.05).

The energetic cost of the 30-min exercise bout of aerobic exercise was extrapolated from steady-state measurements during the first 15 min of the bout in an exercise calorimetry chamber (Fig. 3A). This estimate [exercise activity thermogenesis (EAT)], excluding basal energy requirements, was ~2.0 kcal/30-min bout, or ~4% of total daily expenditure. EAT was dependent on body weight (r^2 = 0.59, P < 0.001), which allowed us to crudely estimate EAT as weight was regained during relapse [EAT = (0.0083 × body wt) − 0.604]. Although the cost of the bout increased by ~15% as the lost weight returned, the impact of this gradual elevation on total expenditure was <1%. EAT was included in the NREE of TEE in subsequent component analyses of energy metabolism.

As expected, the calorie-restricted weight loss reduced TEE (Fig. 2B), which primarily reflected a reduction in REE (Fig. 4A). Average TEE increased during the first several days of relapse in both SED and EX rats (P < 0.05; Fig. 2B), and this effect was more profound in SED rats (interaction, P < 0.05). During the relapse period, TEE gradually increased in both SED and EX rats throughout relapse (P < 0.05). On the final day of measurements, TEE was significantly lower in the EX-relapsed than in the SED-relapsed rats by ~7 kcal (Fig. 4B).
week of relapse. At the end of the 8-wk relapse period, exercise did not significantly affect the diurnal fluctuation in RER (Fig. 5A), but it did lead to a significant reduction in 24-h CHO oxidation (Fig. 5B). In SED rats, during the early stages of the relapse to obesity, CHO is the preferred fuel for energy needs, fat is trafficked to lipid depots, and a significant amount of de novo lipogenesis occurs (15). Regular aerobic exercise abrogates one or more aspects of this shift in fuel utilization.

Training performance. An immediate and persistent decline in the training index was observed in EX rats at the initiation of relapse (Fig. 3C). EX rats became less volitionally compliant to the exercise regimen and required technicians to be more proactive in their oversight of the training bout. This aversion to compliance did not appear to be a function of the increasing body weight, as the average training index did not decline while ~80% of the lost weight returned.

Endocrine and metabolite profiles. As has been shown previously, weight loss led to a reduction in plasma insulin, leptin, amylin, and glucagon. Regular exercise did not significantly affect the levels of these hormones measured at the end of the weight maintenance period, and the changes that occurred in these parameters after the first day of relapse also were unaffected by exercise (data not shown). The two groups of weight-reduced rats also did not differ in free fatty acids, TG, or cholesterol. Glucose tended to be higher in EX rats than in SED rats at the end of weight maintenance (11.1 ± 0.8 vs. 8.8 ± 1.2), but this comparison did not reach statistical significance (P = 0.1). After relapse, the adiposity signals of insulin, leptin, and amylin were not significantly different between SED and EX rats (Table 2). In addition, glucose, TGs, free fatty acids, and 24-h urinary corticosterone were similar for the two groups (Table 2).

DISCUSSION

The novel observations from this study are that regular, aerobic, treadmill exercise in male rats countered several metabolic adaptations to weight loss that are known to facilitate weight regain and the eventual relapse to obesity. These effects reduced the rate of regain early in the relapse process and ultimately lowered the defended body weight and fat mass. During weight maintenance, regular endurance exercise reduced the energy gap between the strong drive to eat and the

Table 1. Body composition and adiposity after relapse

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
<th>SED</th>
<th>EX</th>
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<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Body wt, g</td>
<td>579±15*</td>
<td>735±20†</td>
<td>709±14†</td>
<td>641±11‡</td>
</tr>
<tr>
<td>Fat-free mass, g</td>
<td>422±14</td>
<td>468±17</td>
<td>452±15</td>
<td>456±11</td>
</tr>
<tr>
<td>Fat mass, g</td>
<td>157±7*</td>
<td>267±16†</td>
<td>257±17†</td>
<td>184±13*</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>27.2±1.2*</td>
<td>36.3±1.8†</td>
<td>36.1±2.1†</td>
<td>28.6±1.4*</td>
</tr>
<tr>
<td>Bone, g</td>
<td>11.6±0.4</td>
<td>11.8±0.5</td>
<td>12.3±0.4</td>
<td>12.1±0.6</td>
</tr>
<tr>
<td>Bone density, g/cm³</td>
<td>0.320±0.002</td>
<td>0.322±0.002</td>
<td>0.325±0.002</td>
<td>0.317±0.003</td>
</tr>
<tr>
<td>Liver, mg/dl</td>
<td>15.7±0.3*</td>
<td>18.0±0.4†</td>
<td>18.2±0.6†</td>
<td>15.4±0.5*</td>
</tr>
<tr>
<td>RI, g</td>
<td>17.0±1.2*</td>
<td>31.1±1.7†</td>
<td>32.4±1.6†</td>
<td>26.2±1.3‡</td>
</tr>
<tr>
<td>EPI, g</td>
<td>13.4±1.2*</td>
<td>20.4±0.8‡</td>
<td>18.4±1.2‡</td>
<td>15.5±0.8‡</td>
</tr>
<tr>
<td>MES, g</td>
<td>12.7±1.0*‡</td>
<td>17.6±1.2‡</td>
<td>14.9±1.1‡</td>
<td>11.2±0.7*</td>
</tr>
<tr>
<td>Gastrocnemius, g</td>
<td>3.15±0.17</td>
<td>3.07±0.09</td>
<td>3.25±0.10</td>
<td>3.09±0.08</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE and examined by ANOVA, n, no. of rats. SED, sedentary; EX, exercised; RP, retroperitoneal; EPI, epididymal fat pad; MES, mesenteric. Body composition was determined by dual-energy X-ray absorptiometry. When a significant effect was observed, Duncan’s post hoc test for homogeneous groups was performed. Groups with similar symbol designations are not significantly different, P<0.05.
suppressed level of expenditure. On the first day of relapse, exercise attenuated the positive energy imbalance and blunted the shift in fuel utilization that favored rapid, efficient weight regain. At the end of the 8-wk relapse, regular exercise established a different homeostatic balance between intake and expenditure than what was found in the obese or relapsed SED rats. In defense of their lower weight, relapsed EX rats exhib-
the expenditure side of the energy balance equation (21). In the fuel preference, while running wheel access primarily affected sedentary animals. Beyond this additional benefit of the regimen of exercise did not represent a large contribution to TEE. More surprisingly, there appeared to be an adaptive response with exercise to reduce the other components of TEE during weight maintenance such that TEE was similar for SED and EX rats. Finally, neither running wheel access nor the treadmill exercise used in the present study reflects a regular strength training intervention, which may also affect energy balance regulation. This experimental paradigm may provide a good model to explore the differential impact of intervention that varies the type and intensity of the intervention.

The effects of exercise could not be explained by the well-known adiposity signals, leptin and insulin (13, 46). Neither intervention, running wheels or treadmill exercise, ameliorated the exceptionally low levels of these hormones that convey the energy deficit message from the periphery. Rather, it is likely that this regimen of daily exercise affected how this message from the periphery was received. There is growing evidence to suggest that increasing physical activity might enhance hypothalamic sensitivity to these adiposity signals (12, 34) and/or potentiate the postabsorptive response to the satiety signals peptide YY, glucagon-like peptide 1, and pancreatic polypeptide (29). These effects of exercise are thought to be more acute, being mediated by the hypothalamic nutrient sensor, AMP-activated protein kinase (AMPK). Recent studies have shown that acute bouts of intense exercise blunt AMPK’s response to peripheral signals of acute energy deprivation, which in turn reduces the subsequent drive to overfeed (29, 34). In the present study, weight-reduced rats exhibit a diurnal cycle of two metabolic extremes: an unsatisfying period of gorging followed by a prolonged period of deprivation (15). If the acute effects of exercise on this hypothalamic nutrient sensor are recapitulated on a daily basis, it may account for the reduced energy gap during maintenance and the attenuated positive energy imbalance at the beginning of relapse.

This same nutrient sensor, AMPK, is found in the peripheral tissues, responding to low nutrient availability and reduced energy charge by mobilizing fuel stores and enhancing energy production (19). Like peripheral insulin sensitivity, nutrient sensing by AMPK in the periphery appears to be impaired with obesity (15, 37). Both insulin resistance and impaired AMPK sensing contribute to a more global state of metabolic inflexibility (38) that prevents the appropriate adjustment in metabolic regulation in response to a number of metabolic challenges, like fasting, exercise, and overfeeding. The normal response to a large influx of calories is suppressed fat oxidation, enhanced glucose oxidation, and the trafficking of dietary fat to adipose tissue. This shift in fuel utilization provides the quickest, most efficient way to utilize, clear, and deposit excess fuels. This response to a meal or overfeeding is blunted in the obese but reemerges after weight loss (2, 15). In the present study, metabolic inflexibility in the obese manifests as a relatively static state of metabolism that persists throughout the day, with little or no diurnal fluctuation in RER. Weight loss ameliorates some aspects of this metabolic impairment, since both insulin sensitivity and AMPK responsiveness are improved (15, 25). This reversal of metabolic inflexibility contrasts what is seen in younger animals undergoing catch-up growth after food restriction. Catch-up growth in immature
animals is associated with impaired insulin sensitivity and AMPK signaling and a different consequence on metabolic regulation (39). In the case of the postobese, the enhanced metabolic regulation that occurs after weight loss is thought to establish a biological vulnerability to weight regain by providing the regulatory means to better clear, utilize, and store excess fuels (2, 38, 41). The diurnal fluctuation in RER of weight-reduced SED rats is a manifestation of this improved response to ingested calories.

In a previous study, we provided a practical demonstration of this difference in metabolic flexibility by challenging obese and weight-reduced (SED) rats with the exact same caloric excess over a 24-h period (15). The SED rats rapidly consumed, utilized, and stored the meal provision, exhibiting a

![Graph A](image)

**Fig. 5.** Fuel utilization before, during, and after the relapse to obesity. The effect of exercise on the respiratory exchange ratio (RER) and substrate oxidation is presented. A: RER is separated into 12:12-h dark-light cycles. The diurnal pattern was affected by obesity († P < 0.05) and differed between SED and EX rats at the end of weight maintenance. Exercise reduced RER during the 1st wk of relapse (a P < 0.05). B: substrate oxidation was measured in animals that were in energy balance before and at the end of relapse. For each macronutrient [CHO, fat, or protein (PRO)], a,b,c,d groups with the same letter designation were not significantly different (P > 0.05). RER measured every 6 min over the 24-h monitoring period is shown for SED (n = 8) and EX (n = 8) rats at the end of weight maintenance (C) and on the first day of relapse (D). The meal was delivered at the beginning of the dark cycle (3:00 P.M.). The shaded time on the x-axis indicates the range for the dark cycle. Broken lines indicate extended periods of time during which RER was significantly different between the two groups (P < 0.05).

### Table 2. Humoral characteristics and urinary corticosterone

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
<th>SED</th>
<th>EX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, pM</td>
<td>585 ± 75*</td>
<td>794 ± 81†</td>
<td>580 ± 74†</td>
<td>657 ± 67‡</td>
</tr>
<tr>
<td>Leptin, pM</td>
<td>677 ± 223*</td>
<td>1,308 ± 233†</td>
<td>799 ± 148‡</td>
<td>1,119 ± 197‡</td>
</tr>
<tr>
<td>Amylin, pM</td>
<td>13.3 ± 2.1</td>
<td>20.7 ± 6.1</td>
<td>13.7 ± 1.7</td>
<td>17.4 ± 3.2</td>
</tr>
<tr>
<td>Glucagon, pM</td>
<td>43.4 ± 4.3*</td>
<td>65.7 ± 6.7†</td>
<td>50.6 ± 4.2*</td>
<td>49.7 ± 7.8*</td>
</tr>
<tr>
<td>Glucose, mM</td>
<td>7.4 ± 0.3</td>
<td>7.7 ± 0.3</td>
<td>7.1 ± 0.2</td>
<td>7.5 ± 0.6</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>128 ± 11*</td>
<td>185 ± 13†</td>
<td>154 ± 22†</td>
<td>177 ± 20†</td>
</tr>
<tr>
<td>Free fatty acids, μM</td>
<td>562 ± 80</td>
<td>656 ± 45</td>
<td>680 ± 40</td>
<td>657 ± 76</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>100 ± 10</td>
<td>108 ± 5</td>
<td>105 ± 7</td>
<td>97 ± 7</td>
</tr>
<tr>
<td>Corticosterone, μg/day</td>
<td>3.75 ± 0.42</td>
<td>3.78 ± 0.68</td>
<td>2.91 ± 0.43</td>
<td>3.23 ± 0.26</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE and examined by ANOVA. Insulin and leptin were assessed by enzyme-linked immunosorbent assays, and plasma metabolites were determined by colorimetric assays. When a significant effect was observed, Duncan’s post hoc test for homogeneous groups was performed. Groups with similar symbol designations are not significantly different, P < 0.05.
suggest that these rats were not finished with the relapse—relapsed SED rats, but the energy balance data (Fig. 2) are consistent with this alternating cycle of gorging and deprivation. Our observations provide evidence that this intervention increasing physical activity promotes the oxidation of fat and stores carbohydrates (CHO) when they feed, and then increases the availability and utilization of glucose during the deprivation phase of this cycle. As such, the fluctuation of fuel availability and the associated signal of extreme energy deficit occurring during the latter part of the light cycle may be blunted. This exercise—associated shift in fuel utilization is subtle during maintenance, without necessarily affecting 24-h substrate oxidation when the rats are in energy balance. The impact on whole body fuel utilization only emerges when the weight-reduced rats are faced with the metabolic challenge of unlimited food availability at the start of relapse.

An alternative explanation for our observations is that EX rats may have been just as hungry as SED rats, but the bout of exercise, occurring 2 h after meal delivery, may have interrupted their gorging meal pattern. This delay in continued feeding may have allowed more time to generate feedback signals that would satiate the animal before it could overeat to the same extent as the SED rat. Calorie—restricted rats with access to running wheels perform much of their activity in the hours before the delivery of the daily food provision (21). Unlike the present study, little or no effect on food intake during relapse is observed with running wheel use. Interrupting this gorging meal pattern after calorie—restricted weight loss has been shown to affect weight regain, even when the total daily caloric food intake is standardized (45). Furthermore, proactively altering meal patterns can affect daily EI in humans (36). Additional studies are needed to examine how the timing and intensity of the exercise intervention, in relation to meal delivery, impacts energy balance and fuel utilization.

At the end of the study, relapsed EX rats established a new homeostatic steady state at a lower body weight and fat mass. In this respect, the effects of regular treadmill exercise are somewhat similar to the effects of volitional wheel use (21). As in that study, the effects of exercise on adiposity may have been emphasized on visceral fat pads. What is particularly interesting is that the energy balance and fuel utilization profile of relapsed EX rats is more akin to a lean rat. Calorie—restricted rats that maintain their activity are highly regulated and can significantly impact body weight maintenance to relapse. The propensity for physical activity is highly regulated and can significantly impact body weight and adiposity (40). What we find interesting is that previous studies with this paradigm of weight regain did not show a decline in volitional wheel running during relapse. Instead, relapse caused a dramatic change in the diurnal pattern of wheel use (21). The reasons for this differential impact on the two approaches to increase physical activity are unclear, but the disconcerting message from both is that the initiation of relapse may have a detrimental effect on the motivation to continue a regular exercise program.

Perspectives and Significance

In summary, regular aerobic treadmill exercise attenuated the metabolic propensity to regain weight after long-term weight loss, and did so by reducing the rate of regain early in relapse and reestablishing a new homeostatic steady state between intake and expenditure at a lower body weight. The implications of our findings are that exercise may be critical to abrogating the overwhelming hunger pains and/or insatiable desire to eat that plagues individuals after calorie—restricted
weight loss. For most individuals, these signals are too strong to
ignore, and inevitably lead to the failure to stay on their
diet regimen. Because tissues in the periphery are primed to
metabolize and store any caloric excess in a rapid, energeti-
cally efficient manner, even minor or temporary excursions off
the restricted diet can lead to rapid regain and, potentially, a
reduction in the motivation to be physically active. Preventing
the relapse-induced increase in adipocytes may limit the ca-
pacity to store excess fuels during relapse and could have
substantial effects on the rate of regain early in relapse and in
the defended body weight at the end of relapse. The new
homeostatic steady state achieved after relapse is characterized
by an energy balance and fuel utilization profile that is more
reflective of lean animals, rather than obese or relapsed SED
rats. The fact that regular endurance exercise after calorie-
restricted weight loss has such profound effects on energy
balance, fuel utilization, lipid accretion, and peripheral homeo-
static signals may explain why exercise is so critical to weight
regain prevention. Understanding the mechanisms by which
exercise reduces that rate of regain early in relapse, as well as
how it reestablishes the homeostatic balance that defends a
lower weight and adiposity level, is likely to be actively
pursued in future studies.

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