Retention of sedentary obese visceral white adipose tissue phenotype with intermittent physical activity despite reduced adiposity

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1Department of Nutrition and Exercise Physiology, University of Missouri, Columbia, Missouri; 2Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; 3Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee; 4Dalton Cardiovascular Research Center, University of Missouri, Columbia, Missouri; and 5Department of Child Health, University of Missouri, Columbia, Missouri

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Wainright KS, Fleming NJ, Rowles JL, Welly RJ, Zidon TM, Park Y-M, Gaines TL, Scroggins RJ, Anderson-Baucum EK, Hasty AH, Vieira-Potter VJ, Padilla J. Retention of sedentary obese visceral white adipose tissue phenotype with intermittent physical activity despite reduced adiposity. Am J Physiol Regul Integr Comp Physiol 309: R594–R602, 2015. First published July 15, 2015; doi:10.1152/ajpregu.00042.2015.—Regular physical activity is effective in reducing visceral white adipose tissue (AT) inflammation and oxidative stress, and these changes are commonly associated with reduced adiposity. However, the impact of multiple periods of physical activity, intercalated by periods of inactivity, i.e., intermittent physical activity, on markers of AT inflammation and oxidative stress is unknown. In the present study, 5-wk-old male C57BL/6 mice were randomized into three groups (n = 10/group): sedentary, regular physical activity, and intermittent physical activity, for 24 wk. All animals were singly housed and fed a diet containing 45% kcal from fat. Regularly active mice had access to voluntary running wheels throughout the study period, whereas intermittently active mice had access to running wheels for 3-wk intervals (i.e., 3 wk on/3 wk off) throughout the study. At death, regular and intermittent physical activity was associated with similar reductions in visceral AT mass (approximately −24%, P < 0.05) relative to sedentary. However, regularly, but not intermittently, active mice exhibited decreased expression of visceral AT genes related to inflammation (e.g., monocyte chemoattractant protein 1), immune cell infiltration (e.g., CD68, CD11c, F4/80, CD11b/CD18), oxidative stress (e.g., p47 phagocyte oxidase), and endoplasmic reticulum stress (e.g., CCAAT enhancer-binding protein homologous protein; all P < 0.05). Furthermore, regular, but not intermittent, physical activity was associated with a trend toward improvement in glucose tolerance (P = 0.059). Collectively, these findings suggest that intermittent physical activity over a prolonged period of time may lead to a reduction in adiposity but with retention of a sedentary obese white AT and metabolic phenotype.

obesity; exercise; weight cycling; fat; gene expression; inflammation; ER stress

MORE THAN ONE-THIRD OF American adults are obese, and the prevalence of obesity has more than doubled in the past 50 years (24a). Obesity is an important risk factor for insulin resistance, which plays a key pathogenic role in the development of Type 2 diabetes and cardiovascular disease (11, 30). However, the mechanisms that link obesity and insulin resistance remain poorly understood. Visceral white adipose tissue (AT) dysfunction is a characteristic feature of obesity-related insulin resistance, and evidence implicates AT inflammation as a causal link between obesity and insulin resistance (10). Obesity is associated with infiltration of immune cells into AT, thus contributing to AT inflammation and secretion of inflammatory cytokines (13). Accordingly, it is not surprising that interventions that reduce adiposity, such as exercise and diet restriction, are effective in reducing white AT inflammation and oxidative stress (8, 21, 22). However, human data suggest that individuals who lose weight are frequently unable to maintain this weight loss (39). These repeated oscillations in weight, commonly referred to as weight cycling, are shown to increase the risk for development of Type 2 diabetes and cardiovascular disease in some studies (9, 12, 38). Furthermore, recent experimental data from rodents demonstrate that weight cycling, induced by changes in caloric intake, promotes AT inflammation (2).

Although current evidence indicates that oscillations in body weight resulting from diet changes are detrimental to metabolic and AT function in mice (2), whether multiple periods of physical activity, intercalated by periods of inactivity, also lead to weight cycling and AT dysfunction is unknown. There is evidence from rodent (7, 18, 27) and human (25) studies that cessation of physical activity for 7–10 days is sufficient to increase visceral adiposity. It is not uncommon for humans to transition repetitively from periods of high physical activity to periods of inactivity and vice versa over their lifespan. These oscillations in physical activity levels can be driven by many environmental and psychosocial factors, including changes in seasons or job demands (e.g., grant deadlines in the case of academicians). Accordingly, to begin understanding the metabolic consequences of alternating periods of activity and inactivity, we designed a mouse protocol to “mimic” oscillations in physical activity levels that humans often encounter in life. Specifically, intermittently active mice had access to running wheels for 3-wk intervals (i.e., 3 wk on/3 wk off) throughout a 24-wk period. First, we hypothesized that intermittent physical activity would result in corresponding oscillations in body weight, not unlike “yo-yo dieting.” Second, although regular exercise exerts strong anti-inflammatory and antioxidant effects on AT (5, 6, 8, 15, 16, 20, 36), we hypothesized that intermittent physical activity—and thus associated fluctuations in body weight—would not lead to an improved AT phenotype. In particular, we sought to examine in visceral white AT markers of inflammatory adipokines, oxidative stress, endoplasmic reticulum (ER) stress, and immune cell infiltration. To
determine if the observed effects of intermittent physical activity were specific to AT, the same mRNA markers were assessed in the liver, another metabolically active tissue.

METHODS

Experimental design. Male C57BL/6 mice (n = 30), from The Jackson Laboratory (Bar Harbor, MA), arrived to our facility at 4 wk of age and after 1 wk of acclimatization, were randomized to three groups (n = 10/group): sedentary, regular physical activity, and intermittent physical activity, for 24 wk. All mice were singly housed under standard temperature conditions (~22°C) and humidity with a light cycle from 0700 to 1900 and a dark cycle from 0700 to 0700. All mice were fed a diet containing 45% kcal from fat (Product #D12451; Research Diets, New Brunswick, NJ) ad libitum. Regularly active mice had access to voluntary running wheels throughout the 24-wk study period, whereas intermittently active mice had access to running wheels for 3-wk intervals (i.e., 3 wk on/3 wk off) throughout the study period (four total cycles, with each cycle ending with inactivity). Running wheels were connected to a Sigma BC509 cycling computer (Product #CP244A02; Jenson USA, www.JensonUSA) for determination of weekly running distance. Food intake and body weight were also assessed weekly throughout the study. At 29 wk of age, mice were euthanized via CO₂ inhalation, and tissues were harvested for downstream analysis. Before death, the wheels of the regularly active mice and food from all mice were removed from the cages for ~12 h. All animal protocols were approved by the University of Missouri Institutional Animal Care and Use Committee.

Fasting blood parameters. Glucose, cholesterol, triglycerides, and nonesterified fatty acid assays were performed by a commercial laboratory (Comparative Clinical Pathology Services, Columbia, MO) on an Olympus AU680 automated chemistry analyzer (Beckman-Coulter, Brea, CA) using assays, according to the manufacturer’s guidelines. Plasma insulin concentrations were determined using a commercially available, mouse-specific ELISA (Alpco Diagnostics, Salem, NH). The whole-blood samples were analyzed for HbA1c using a boronate affinity HPLC method, ultra2 (Triumph Biotech, Kansas City, MO). This method measures all glycated Hb by binding to the cis-diol groups of the glucose bound to Hb. The method is standardized following the National Glycohemoglobin Standardization Program to report HbA1c specifically.

Glucose-tolerance tests. Glucose-tolerance tests were performed at 17 wk of age. In brief, after an overnight fast, blood glucose was measured from the tail vein. The tail was nicked, and blood was sampled by a hand-held glucometer (AlphaTRAK; Abbott Laboratories, Abbott Park, IL). A baseline measure of blood glucose was taken before giving a sterile solution of 50% dextrose (2 g/kg body wt) via intraperitoneal injection, as performed previously (35, 36a). Glucose measures were taken, 15, 30, 45, 60, and 120 min after the glucose injection. Glucose area under curve from baseline was calculated.

Statistical analysis. One-way ANOVA was used to compare the means of the three independent groups of animals (sedentary, regularly active, and intermittently active mice) for all dependent variables and followed by a least-significant difference post hoc test for pairwise comparisons. All data are presented as means ± SE. For all statistical tests, the alpha level was set at 0.05. All statistical analyses were performed with SPSS V22.0.

RESULTS

As shown in Fig. 1A, mice with continuous access to running wheels increased running distance throughout the first 3 wk of the study (peak running distance 2150 km/wk at 8 wk of age), and then running distance gradually declined to 81 km/wk by 29 wk of age. Mice with intermittent access to running wheels also exhibited a decline in running distance over time; however, during the periods of wheel access, the running distance in intermittently active mice was greater than that of regularly active mice. The total running distance over the 24-wk period was 1,417 ± 153 km for regularly active mice and 1,042 ± 102 km for intermittently active mice (P = 0.056). Regular physical activity attenuated the age and high-fat, diet-related increase in body weight relative to sedentary mice (Fig. 1B). Intermittent physical activity appeared to produce mild fluctu-
ations in body weight, but these fluctuations subsided over time, resulting in the attenuation of body weight similar to that of mice engaged in regular physical activity (Fig. 1B). As shown in Fig. 1C, regularly active mice ate more food than sedentary mice. Food intake of intermittently active mice “cycled” in parallel with their activity levels. That is, in periods of activity, they ate a similar amount to that of regularly active mice, whereas in periods of inactivity, they ate a similar amount to that of sedentary mice. Accordingly, the average food intake over the course of the 24-wk period for the intermittently active mice was in between the regularly active and sedentary mice (see Fig. 1C).

As illustrated in Fig. 2A, final body weights were ~12% lower in the regular (P < 0.05) and intermittent (trending P = 0.069) physically active mice compared with the sedentary mice, but regular and intermittent exercisers were not different from each other (P > 0.05). Additionally, both regular and intermittent physically active mice had reduced visceral white (i.e., retroperitoneal and epididymal) and brown AT mass compared with sedentary mice (P < 0.05; Fig. 2, B, C, and E). As markers of training adaptation, heart weight-to-body weight ratio was increased with both regular and intermittent physical activity (P < 0.05; Fig. 2F), and citrate synthase activity in the soleus muscle tended to be higher in both groups of physical activity but did not reach statistical significance (P > 0.05; Fig. 2G). In addition, regular physical activity was associated with improved glucose tolerance (Fig. 2I) relative to intermittently active mice. Glucose tolerance of intermittently active mice was similar to that of sedentary obese mice (P = 0.6; Fig. 2I). As summarized in Table 2, compared with sedentary mice, regular and intermittent physical activity similarly reduced fasting plasma LDL cholesterol (P < 0.05). However, regular but not intermittent physical activity reduced fasting plasma insulin (P < 0.05).

Figure 3 summarizes the effects of regular and intermittent physical activity on retroperitoneal AT gene expression and AT mass. Regular physical activity was associated with reduced retroperitoneal AT mass and reduced mRNA levels of genes related to inflammation [e.g., monocyte chemoattractant protein 1 (MCP1)], immune cell infiltration (e.g., CD68, CD11c, F4/80, CD11b/CD18), oxidative stress [e.g., p47 phagocyte oxidase (phox)], and ER stress [e.g., CCAAT enhancer-binding protein homologous protein (CHOP)] compared with sedentary mice. Similar nonsignificant trends were observed for mRNA levels of other markers of inflammation, oxidative stress, and ER stress [e.g., IFN-γ, CCR2, regulated on activation, normal T cell expressed and secreted (RANTES), Leptin, p22phox, and glucose-regulated protein 78 (GRP78); Fig. 4]. In contrast, although intermittent physical activity was also associated with reduced retroperitoneal AT mass, as in the continuously active group, this weight loss was not accompanied by a reduction in expression of several inflammatory, oxidative, and ER stress markers (P > 0.05 compared with sedentary group; Fig. 3).

Figure 4A illustrates representative histological images of epididymal white AT stained with Mac-2, a macrophage marker. Although adipocyte size was similar among groups (Fig. 4, B and C), in support of the inflammatory gene-expression differences between active groups, the AT of the regularly active mice tended to have fewer crown-like structures per field of view (indicative of adipocyte necrosis and inflammation) compared with the intermittently active mice (P = 0.054; Fig. 4D).

Representative images of Oil Red O-stained liver sections are presented in Fig. 5A. A reduced amount of Oil Red O staining in regularly and intermittently active mice compared with sedentary mice is consistent with the decrease in liver triglycerides (P < 0.05; Fig. 5B). The same RNA markers reported in Fig. 3 (in AT) were measured in the liver and are summarized in Fig. 5C. No significant changes in liver gene expression were found across all genes examined.

DISCUSSION

In the present study, we compared mice trained continuously on running wheels with mice exposed to running wheels intermittently (i.e., 3 wk on/3 wk off for a 24-wk period). We demonstrated that mice intermittently exposed to running dis-
played a reduction in visceral adiposity that was comparable with that observed in animals that had constant access to running wheels. However, the reduction in adiposity caused by intermittent physical activity was not accompanied by a reduction in expression of inflammatory genes in visceral white AT to the level exhibited by mice undergoing continuous exercise training. Furthermore, we found that regular but not intermittent physical activity was associated with a modest improvement in glucose tolerance. Together, these findings suggest that intermittent physical activity over a prolonged period of time may lead to a reduction in adiposity, albeit with retention of a sedentary obese white AT and metabolic phenotype.

Emerging evidence implicates white visceral AT inflammation as a contributor to the development of obesity-related metabolic disease, such as Type 2 diabetes and cardiovascular disease (11, 37). It is now recognized that visceral white AT is a source of a plethora of proinflammatory cytokines that are magnified in the setting of obesity (13). Indeed, obesity is associated with infiltration of immune cells, such as macrophages and T lymphocytes, which can crossactivate one another and perpetuate the secretion of inflammatory cytokines from AT (26). Effective approaches to reduce AT inflammation and secretion of proinflammatory cytokines associated with obesity include increased physical activity and diet restriction, likely as a result of decreased adiposity (22). As such, current evidence indicates that anti-inflammatory effects of diet-induced weight loss manifest when decreased adiposity is sustained over time (19, 39). In this regard, a recent study in mice, by our coauthors Anderson (Baumc) and Hasty and their colleagues (2), demonstrated that weight loss and weight regain by alternating high-fat and low-fat diets resulted in a proinflammatory stimulus to AT. However, to date, it remained unknown whether fluctuations in body weight, induced by alternating periods of physical activity and inactivity, rather than changes in the dietary composition, would also pose a proinflammatory insult to AT. To begin to understand the metabolic consequences of alternating periods of activity, we designed a mouse protocol to mimic oscillations in physical activity that humans often encounter in life. Specifically, we studied high-fat, diet-fed mice that were exposed to running wheels during 3-wk periods every 3 wk for a total of 24 wk and compared them with mice that remained physically active or sedentary throughout the entire study period.

Contrary to our expectation that intermittent episodes of physical activity would lead to pronounced fluctuations in body weight, only small oscillations in body weight were apparent during the initial weeks of activity and subsided over time. Notably, at the conclusion of the study, we found that intermittent activity led to a reduction in body weight and AT mass compared with that found with regular physical activity (Figs. 1B and 2). As noted, the reduction in visceral adiposity with regular and intermittent physical activity was also associated with reduced ectopic liver fat (Fig. 5, A and B). It is possible that the similar reductions in adiposity achieved by both exercise regimens were due to the fact that animals undergoing intermittent activity ran more (i.e., had greater energy expenditure) during the periods of wheel access compared with the animals with constant access to running wheels. Thus whereas the total running distance of intermittently active mice was slightly less than that of regularly active mice, intermittently active mice also ate slightly less than the regularly active mice. However, this difference in average food intake was not statistically significant (Fig. 1C). The greater running of intermittently active mice when exposed to running wheels may be related to a “novelty phenomenon,” which may also explain why running distance markedly declines over time in most rodents chronically exposed to running wheels (Fig. 1A) (8, 24, 33).

The most salient finding of the present study is that even though intermittent physical activity caused a reduction in body weight and adiposity, similar to that induced by regular activity, this was not accompanied by a decrease in inflammatory gene expression and markers of macrophage cell infiltration in visceral white AT (Figs. 3 and 4). However, reductions in adiposity induced by regular activity did produce the expected significant reduction in expression of a number of genes related to inflammation (e.g., MCP1), immune cell infiltration (e.g., CD68, CD11c, F4/80, CD11b/CD18), oxidative stress (e.g., p47phox), and ER stress (e.g., CHOP; Fig. 3). As noted in Fig. 3, other mRNAs, such as IFN-γ, CCR2, RANTES, Leptin, p22phox, and GRP78, also displayed a downregulation with regular but not intermittent physical activity; however,
these effects did not reach statistical significance, likely due to lack of statistical power. Similar trends were noted in the number of Mac-2-stained, crown-like structures (Fig. 4D).

Thus the phenotype of visceral white AT from animals exposed to intermittent activity recapitulates that of the sedentary obese animals, despite the reduced AT mass. Therefore, although the mechanisms remain to be investigated, it appears that intermittent activity produces a leaner but inflammatory obese visceral AT phenotype, while continuous activity also decreases AT inflammation. Notably, the glucose tolerance of these lean animals also resembled that of sedentary obese animals (Fig. 2I), supporting the notion that white visceral AT inflammation is associated with metabolic dysfunction. However, future studies are needed to determine if these changes in glucose tolerance translate to changes in insulin resistance by incorporating insulin-tolerance tests or hyperinsulinemic clamps. Another observation that should be noted is that this differential modulation of AT phenotype with regular vs. intermittent physical activity cannot be extrapolated to other metabolically active tissues. Indeed, as we show in Fig. 5C, expression of genes reported to be modulated in AT (Fig. 3) was largely unaffected in the liver.

Table 2. Fasting blood characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sedentary</th>
<th>Regular Physical Activity</th>
<th>Intermittent Physical Activity</th>
</tr>
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<tbody>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>152.1 ± 13.1</td>
<td>125.0 ± 13.8</td>
<td>121.0 ± 13.2</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>6.9 ± 0.9</td>
<td>4.1 ± 0.5*</td>
<td>4.4 ± 1.0*</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>56.8 ± 3.2</td>
<td>54.7 ± 6.2</td>
<td>50.6 ± 3.6</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>96.5 ± 6.5</td>
<td>83.4 ± 8.8</td>
<td>77.9 ± 9.4</td>
</tr>
<tr>
<td>NEFA, mmol/l</td>
<td>1.06 ± 0.07</td>
<td>0.91 ± 0.10</td>
<td>1.01 ± 0.15</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td>1.08 ± 0.26</td>
<td>0.42 ± 0.11*</td>
<td>0.58 ± 0.25</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>273.8 ± 30.2</td>
<td>220.3 ± 37.8</td>
<td>204.5 ± 41.6</td>
</tr>
<tr>
<td>% HbA1c</td>
<td>4.42 ± 0.10</td>
<td>4.62 ± 0.04</td>
<td>4.58 ± 0.06</td>
</tr>
</tbody>
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NEFA, nonesterified fatty acids. *P < 0.05, difference from sedentary mice. Values are expressed as means ± SE.
type, thus supporting the notion that the magnitude of adiposity is not the sole factor dictating AT function. Furthermore, the observation that despite reduced adiposity and liver fat, intermittent physical activity did not lead to improvements in glucose tolerance may support the idea that the molecular phenotype of visceral AT is an important determinant of whole body metabolic function. In this regard, various animal models exist demonstrating that AT-specific genetic manipulation can have profound metabolic effects, independent of adiposity (17). Along these lines, recent data by Goodyear’s group (32) demonstrate that sedentary mice receiving an AT transplant from exercise-trained mice improve their glucose tolerance 9 days later.

In the present study, intermittently active mice were studied after a 3-wk period of inactivity. We expected that removal of activity would create a weight-rebound effect, such that final body weights would be similar to that of chronically sedentary animals. Instead, to our surprise, the weight and AT mass matching occurred between the two groups of exercising animals, also creating an attractive situation for studying the effects of continuous vs. intermittent physical activity, independent of adiposity. Based on the current study design, however, we cannot rule out that the effects of intermittent physical activity may relate simply to the last 3 wk of inactivity before death. We acknowledge that inclusion of an extra group of mice undergoing regular physical activity with removal of activity during the last 3 wk would have strengthened the study. Nevertheless, an important aspect to consider here is that if the effects of intermittent physical activity were solely explained by the last 3 wk of inactivity, then one would have expected an increase in visceral adiposity relative to the regularly active mice. Indeed, we (8) and others (7, 18) have shown...
that even 1 single wk of cessation of wheel running in rodents increases visceral fat-pad weights, and this is also the case in humans (25). The fact that intermittently active mice, after the last 3 wk of inactivity, were not fatter than the regularly active mice suggests that oscillations in activity over time may lead to a distinct phenotype that may not recapitulate the effects of only 3 wk of inactivity. However, this is speculative, and additional experimentation is warranted to test this important hypothesis. Furthermore, additional studies are needed to elucidate the mechanisms by which intermittent activity leads to this puzzling association between reduced AT mass and an “unhealthy” AT molecular signature. Based on the observation that oscillations in body weight were not prominent and were clearly attenuated toward the end of the study, one may conclude that weight cycling per se was not the primary driving factor for this AT maladaptation. Indeed, these AT effects appear to be mediated by “exercise cycling” instead of “weight cycling.” However, it remains possible that AT exhibited oscillations in mass, which were undetectable with measures of body weight. In this regard, future studies examining the effects of intermittent exercise should include periodic noninvasive measures of percent body fat. As is the case with most exercise-training studies, it is possible that some of the observed exercise effects on AT gene expression were the result of a residual acute effect from the last bout of exercise and not reflective of a chronic exercise-induced AT adaptation. To alleviate this concern, as is customary, running wheels were removed from the cages of regularly active animals, ~12 h before death.

Fig. 4. Representative histology images (10×) of visceral white (i.e., epididymal) AT stained for Mac-2 (A), adipocyte cell size (B and C), and number of crown-like structures (D) in sedentary mice and mice engaged in regular vs. intermittent physical activity. Values are expressed as means ± SE.

Fig. 5. Representative histology images (20×) of Oil Red O-stained liver (A), liver triglycerides (TG; B), and liver gene expression (C) in sedentary mice and mice engaged in regular vs. intermittent physical activity. Values are expressed as means ± SE. *P < 0.05, difference from sedentary.
Perspectives and Significance

In conclusion, the present data suggest, for the first time, that intermittent physical activity over a prolonged period of time may lead to the retention of a sedentary obese white AT and glucose-intolerant phenotype, despite a reduction in adiposity. These findings highlight the importance of uninterrupted (i.e., regular) physical activity for sustaining AT and metabolic health.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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