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IT IS NO SECRET THAT OBESITY and obesity-related metabolic disorders are rising unabated in the United States (5, 6), and this epidemic has not eluded children. From 1999–2000 to 2003–2004, the prevalence of overweight children/adolescents increased from 13.8 to 16.0% for males and 14.0 to 18.2% for females (13). Of the three major actual causes of death (tobacco, poor diet, and physical inactivity) as classified by the Centers for Disease Control (12), physical inactivity has received the least attention.

One paradigm of physical inactivity is based on the premise that physically active subjects (or animals) should be the control group (2). Using a young animal model consuming 17% of their diet as fat calories, Booth and colleagues have established in a series of eloquent studies that incorporation of voluntary running wheel lock, inducing physical inactivity (for ~2 days) after a period of voluntary physical activity (>3 wk), results in a rapid loss of submaximal insulin stimulated 2-deoxyglucose uptake into epididymal muscle, mediated, at least in part, through decreases in insulin receptor β-subunit protein, insulin receptor β-subunit tyrosine phosphorylation, GLUT4 and Akt phosphorylation (7), and a rise in palmitate incorporation into triglyceride (TG; an index of triglyceride synthesis) in epididymal adipose tissue (8), mediated, in part, by an increase in mitochondrial glycerol-3-phosphate acyltransferase, a key regulator of TG synthesis (9). These changes were associated with increases in both plasma insulin and TG ~2 days after wheel lock. Additionally, this group noted an increase in abdominal fat accumulation after ~2 days of wheel lock. In these studies, animals were fed ad libitum and consumed more food than sedentary rats during activity and wheel-lock phases, raising the possibility that the increase in abdominal adiposity was simply due to the inability of the animals to acutely regulate their food intake with inactivity, resulting in caloric excess.

In their current study in this issue of the Journal of Applied Physiology, Laye et al. (10) set out to determine whether (1) the increase in abdominal adiposity was simply a function of excess food intake during wheel lock; (2) extension of the wheel lock would indicate a transient effect; and (3) an increase in abdominal fat was maintained, and whether the increase in abdominal fat noted was explained by an increase in adipocyte hypertrophy and/or hyperplasia. To test these hypotheses, the authors employed a pair-feeding model and a 1-wk wheel-lock phase.

Laye et al. (10) noted two significant findings. First, enlargement of fat mass occurred with both ad libitum and pair feeding, suggesting that the effects were not simply due to the overconsumption of food. Ironically, food intake in the ad libitum-fed group returned to sedentary values by the fourth day of wheel lock, indicating that pair-fed and ad libitum groups consumed similar calories after the fourth day (Fig. 2, A–D). Additionally, most of the increase in fat occurred between the second and seventh day of wheel lock (Fig. 3, A–C). During the 7-day period of wheel lock, the increase in body size was only 0.5% in the pair-fed group and 3.5% in the ad libitum group, suggesting that the large increases in fat mass noted were largely independent of body mass. The data that increased fat mass occurred when normalized to body mass support this contention. Taken together, these data indicate that the increase in abdominal fat was not due to the inability of this rat model to regulate its food intake.

Second, these authors noted rapid adipocyte hyperplasia (Fig. 6), but not hypertrophy (Figs. 4 and 5), in this model. During the period of voluntary running, body mass increased fivefold, but voluntary running restricted the growth of fat in proportion to body mass. These results are very provocative given the conventional view that early changes in fat are thought to be mediated predominately by adipocyte hypertrophy (14).

What was responsible for the rapid increase in fat stores and fat cell hyperplasia? It is possible that evolutionary programs are evoked by intermittent periods of inactivity to facilitate fat stores. That is, when fat mass is proportionally less than homeostatic for body mass, there may be a survival mechanism activated such that when excess calories reoccur, preadipocytes respond by hyperplasia. This response is not surprising. In a previous study (15), we speculated that the homeostatic drive for food may play a role in the reestablishment of body fat stores and energy homeostasis. Similarly, the drive to reestablish energy stores may facilitate fat deposition after periods of inactivity, because of enzymatic adaptations (9). This may be analogous, to a degree, to the restoration of glycogen after its acute depletion via carbohydrate restriction and exercise, resulting from enzymatic adaptations, as the body tries to return glycogen to homeostatic levels. A similar mechanism may occur with physical activity in which the body may sense decreased fat stores and the desire to maintain homeostatic levels in the face of any future caloric deficit that is countered by an increased number of adipocytes, which theoretically could store more lipid in times of caloric excess. A recent report by MacLean et al. (11) found a similar response in a different model where obesity-prone rats were caloricly restricted; on the presentation of ad libitum food, adipocyte number and fat mass overshot cohorts never experiencing the food restriction. Because the proteins C/enhancer binding protein-β, C/enhancer binding protein-α, and peroxisome proliferator-activated receptor-γ play a role in adipogenesis (14), they desire future study. Interestingly, Laye et al. (10) analyzed only the epididymal fat for hyperplasia, which exhibited the lowest percent increase in fat mass of the three fat pads, suggesting that even relatively smaller increases in fat mass exhibit hyperplasia.

Others have described the recovery of adiposity from a low proportion of fat to body mass in humans as “adiposity rebound.” Adiposity rebound has been noted in children, and it increases the risk of future obesity (3, 16), glucose intolerance (1), and diabetes (4). The activity to inactivity transition and the resulting increase in fat might be analogous to adiposity rebound. Indeed, adiposity rebound has been attributed to periods of physical inactivity in humans (17). Physical activity in the Laye et al. (10) article slowed the growth of abdominal adipose tissue, and the ensuing period of physical inactivity permitted fat cell hyperplasia that was even greater than in animals never exposed to wheel running. It is conceivable that inactivity early in life may program “thrifty” genes that will exert adverse metabolic consequences later in life.
more, one can speculate that minicycles of adiposity rebound with chronic activity and inactivity over a period of years could incrementally increase adipocyte number above those without such cycling. This speculation is based on the priority of selection pressures to efficiently store calories as fat after decreases in fat mass in the event of future caloric insufficiency. A similar mechanism may also explain the commonly noted weight regain that occurs with repeated dietary cycling.

The findings of Laye et al. (10) raise many questions for future studies. What is the long-term effect of repeated activity-inactivity transitions on fat cell number? Does chronic inactivity lead to the same adaptation to increase adipose tissue mass? Do older animals gain fat during periods of inactivity as rapidly? Additionally, the effects of inactivity transitions in humans remain to be determined. This animal model may provide insight into adiposity rebound mechanisms given difficulties in obtaining fat biopsies from youth. Nevertheless, the provocative report by Laye et al. provides evidence that we need to recognize that adaptations resulting from transitioning from activity to inactivity are likely distinct from the inactivity to activity transition, and they may have deleterious consequences that increase future chronic disease risk.

REFERENCES

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