COMMENTARY

Sexual Dimorphic Effects of Exercise Training on Subcutaneous White Adipose Tissue of Mice

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Obesity is estimated to affect more than 600 million people worldwide (1). The strong relationship between obesity and multiple diseases, including type 2 diabetes, has motivated ongoing research aimed at understanding the fundamental biology of adipose tissue. Adipocytes can be characterized as white, brown, or beige. White adipocytes are crucial for energy (triglyceride) storage (2). White adipocytes also release numerous signaling molecules (adipokines) that have endocrine, paracrine, and/or autocrine functions. Distinctive physiological purposes and metabolic features have been documented for visceral versus subcutaneous white adipose tissue (WAT) depots (3). The primary feature of brown adipocytes is their exceptional capacity for heat generation. Beige adipocytes, which are interspersed in WAT depots, also have substantial thermogenic capacity. However, brown and beige adipocytes arise from distinct lineages (4). A variety of interventions, including exposure to cold ambient temperature, β-adrenergic activation, and physical exercise, can stimulate the induction and activation of beige adipocytes. Unraveling the remarkable complexity and adaptive potential of adipose tissue continues to be a crucial, but challenging, task.

Research performed 30–40 years ago revealed that in rats, chronically performed exercise can modify metabolic properties of WAT, including insulin-stimulated glucose uptake and the activity of mitochondrial enzymes (5,6). Nonetheless, it was remarkable when recent research from the Goodyear laboratory reported that only 11 days of voluntary wheel running activity altered the expression of thousands of genes (increased expression of >1,500 genes and reduced expression of >1,100 genes) in the inguinal subcutaneous WAT (iWAT) of mice (7). Most of the published studies that have focused on the metabolic and molecular consequences of exercise on WAT in rodents have not included both sexes. Several influential early studies included only females (5,6). Recent research that characterized exercise effects on gene expression was limited to males (7). Accordingly, the extent to which exercise training effects on WAT biology are sex specific is a prime target for rigorous study.

In this issue of *Diabetes*, Nigro et al. (8) evaluated the influence of exercise training on WAT from both female and male mice. Compared with male mice, female mice ran ∼17% greater distance per day when given access to a voluntary running wheel for 11 days. Surprisingly, despite the greater distance run by females compared with males, adipose tissue adaptations were detected only in the male mice. In response to exercise training, only the male mice had a significant reduction in the mass of whole-body fat, iWAT, epigonadal WAT, and intrascapular brown adipose tissue. Subsequent analyses focused on the iWAT because prior research suggested that this depot can substantially influence systemic metabolism (7). Exercise training resulted in enhanced mitochondrial function and expression of mitochondrial genes as well as the induction of beiging (including elevated expression of UCP1 and Cidea) in the iWAT of male mice but not of female mice. Analysis of iWAT gene expression revealed that exercise training increased the expression of several genes for androgen receptor coactivators in males but not females. Another novel finding was that either exercise training or incubation of iWAT with testosterone led to greater mRNA expression of Crisp1 (cysteine-rich secretory protein 1) only in males. Furthermore, incubation of iWAT with testosterone induced the secretion of CRISP1 protein only for males, and this effect was blocked by an androgen receptor antagonist. Serum CRISP1 protein concentrations were many-fold greater for male versus female mice but were unaltered by exercise in either sex. Incubating adipose-derived stem cells with CRISP1 protein induced the expression of multiple markers of beiging. In cultured 3T3-L1 cells, incubation with CRISP1 protein increased glucose and fatty acid uptake. Taken together, the results of this study revealed markedly

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different exercise-induced adaptations in the iWAT from male mice compared with female mice.

The most important aspect of this study was the evaluation of metabolic phenotype and gene expression of both female and male mice in response to exercise training. Another notable strength was the identification of an androgen-related mechanism that contributed to the striking sexual dimorphic response of iWAT to exercise training. An additional significant outcome of the study was the discovery of a novel, exercise-responsive and sex-specific adipokine, CRISP1. A limitation of the study was that the influence of endurance training on glucose tolerance and insulin sensitivity was not determined. Therefore, it is unclear whether the dramatic sex-specific differences in adipose tissue adaptations were important for exercise-induced modifications in whole-body glucoregulation. This uncertainty is notable in the context of an earlier study of male mice that were subjected to a similar exercise training program as was used in the current study (9). Some of the mice in the earlier study underwent lipectomy that eliminated their iWAT. The results indicated that exercise training induced comparably improved glucose tolerance and insulin tolerance for lipectomized mice compared with sham surgery controls. These findings suggest that iWAT may not be essential for these metabolic outcomes. Accordingly, future research is required to fully understand the implications of the results of the current study for whole-body glucoregulation. Another caveat of the current study was that the physiological importance of CRISP1 was not assessed. However, the results in 3T3-L1 cells provide compelling, preliminary evidence to justify future research (e.g., using mice with WAT-specific deletion of CRISP1 or WAT-specific overexpression of CRISP1) to fill this gap in knowledge.

Research on the effects of exercise on adipose tissue continues to provide unexpected and important results. The observations of Nigro et al. (8) have significantly advanced this unfolding story. It is crucial for future research to pursue the mechanisms responsible for, and the functional consequences of, the marked sex-specific differences in iWAT adaptations to exercise training in mice. Moreover, this preclinical study provides a further incentive for the systematic pursuit of knowledge related to the metabolic consequences of exercise on both women and men.

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