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Exercise-induced intertissue communication: adipose tissue and the heart

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Exercise leads to numerous beneficial whole-body effects and can protect against the development of obesity, cardiometabolic, and neurodegenerative diseases. Recent studies have highlighted the importance of inter-tissue crosstalk with a focus on secretory factors that mediate communication among organs, including adipose tissue and the heart. Studies investigating the effects of exercise on brown adipose tissue (BAT) and white adipose tissue (WAT) demonstrated that adipokines are released in response to exercise and act on the heart to decrease inflammation, alter gene expression, increase angiogenesis, and improve cardiac function. This review discusses the exercise-induced adaptations to BAT and WAT and how these adaptations affect heart health and function, while highlighting the importance of tissue crosstalk.

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Introduction

Exercise is an important therapeutic tool that can prevent or delay the onset of obesity, type 2 diabetes, and cardiovascular disease [1–3]. Acute bouts of moderate intensity exercise can activate metabolic pathways that have a positive downstream effect for whole-body glucose homeostasis, improved insulin tolerance [4,5], and even play a role in cardiorespiratory fitness [6]. Exercise has beneficial effects on multiple tissues, and several studies have demonstrated the beneficial effects of exercise on adipose tissue. Most recently, studies have shown that exercise alters the endocrine capabilities of adipose tissue [5,7]. These exercise-induced secretions from adipose tissue facilitate inter-organ crosstalk, including communication from adipose tissue to skeletal muscle, liver, and the heart [7,8]. Here, we will discuss how the exercise adaptations to adipose tissue mediate heart health and function.

Adipose tissue

There are three distinct types of adipose tissue in humans and rodents: brown adipose tissue (BAT), white adipose tissue (WAT), and beige adipocytes. For this review, we will primarily focus on exercise-induced adaptations to BAT and WAT and how those affect cardiovascular function and health (Fig. 1).

Brown adipose tissue (BAT)

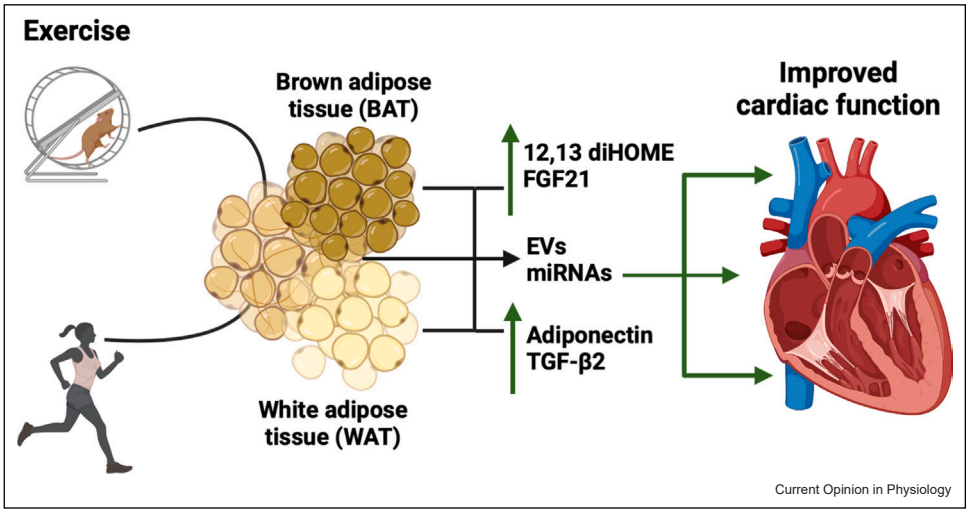
BAT is highly vascularized with an abundance of sympathetic nerves [9]. It acts primarily as a thermogenic tissue that dissipates energy in the form of heat, and this is driven by the presence of uncoupling protein 1 (UCP1) [10]. UCP1 resides in the inner membrane of mitochondria and works by displacing the proton gradient potential, and this discharge of the gradient results in the generation of energy in the form of heat [11,12]. In humans, BAT is found in the cervical, supraclavicular, axillary, and paravertebral regions [13], whereas, in rodents, BAT is found in cervical, interscapular, mediastinal, perirenal, and axillary regions [14].

Recent studies have demonstrated the importance of BAT as a therapeutic target for cardiometabolic disease in humans and rodents [5,15–17]. While the mechanism for this has not been fully elucidated, work from our laboratory has identified the endocrine function of BAT to be critical in this response [18]. BAT releases lipokines or adipokines in response to stimuli, including cold or exercise that can improve cardiometabolic health [19,20], and these are discussed in detail below.

White adipose tissue

WAT is composed of white adipocytes as well as several other cell types, and its primary functions are insulation and energy storage [21]. There are multiple WAT depots, which can be broadly subdivided into subcutaneous adipose tissue (scWAT) and visceral adipose tissue (vWAT). These adipose tissue depots store lipids in the form of triglycerides, which can then be mobilized and used for

Figure 1



Exercise-induced adaptations to BAT and WAT promote adipokine secretions to improve cardiac function.

energy [22]. scWAT is located beneath the skin, and is associated with improved insulin sensitivity and glucose tolerance [23]. vWAT is predominantly found in the abdominal cavity, where it lines internal organs, and has been correlated with insulin resistance [24]. Similar to BAT, WAT also acts in an endocrine manner by secreting adipokines, micro-RNAs (miRNAs), and extracellular vesicles (EVs) [25,26], which is particularly important for communication with the heart.

Beige adipocytes

Beige adipocytes are found within WAT depots, and contain small lipid droplets, mitochondria, and express UCP1 [27]. Beige adipocytes stem from white adipocytes and are identified by beiging markers *CD137*, T-box transcription factor 1, and transmembrane protein 26 [28]. In the absence of stimuli to induce beiging, they can return to white adipocytes, highlighting their plasticity. These adipocytes function similarly to brown adipocytes where they generate energy in the form of heat, and their ability to adapt is arguably important for mediating metabolic diseases.

Excercise and adipose tissue

Exercise is an important tool to prevent the development of cardiometabolic disease and induces adaptations to skeletal muscle and the heart. Different exercise intensities result in different adaptations, throughout this review, we will present data from studies investigating both moderate- and high-intensity exercise. Moderate-intensity exercise is when an individual is working at 50–70% of the maximum heart rate, while high- or vigorous-intensity exercise is considered to be 70–85% of maximum heart rate [29]. Adipose tissue is highly dynamic and able to respond to changes in energy demands, such as exercise with acute and chronic adjustments. These adaptations come as a result of exercise stimulating adipose tissue to secrete the necessary adipokines, thus affect systemic homeostasis, and help prevent cardiometabolic diseases.

Effects of exercise on brown adipose tissue

Despite BAT being the most metabolically active adipose tissue, the studies investigating exercise-induced adaptations to BAT have been conflicting. Exercise increases energy expenditure, and indirectly increases thermogenesis, which results in the activation of BAT, but most studies indicate that exercise does not enhance glucose uptake in BAT. In humans, multiple studies have looked at various exercise intensities and found that moderate- but not high-intensity exercise improved glucose metabolism in BAT [30]. Vosselman et al. demonstrated that BAT activity, measured by cold-stimulated glucose uptake, was reduced in male endurance athletes compared with body mass index matched sedentary males [31]. These findings suggest that endurance exercise does not stimulate glucose uptake in BAT. Most recently, the ACTIBATE study investigated the effects of exercise on BAT in male and female human subjects using a randomized control trial to assess BAT activity after 24 weeks of combined endurance and resistance training protocol [32]. Similar to previous studies, there was no effect of exercise on BAT volume or glucose uptake.

In rodents, studies investigating the effects of exercise on BAT have also provided conflicting data. One study found that when high-fat diet-fed mice were given open access to voluntary wheel running cages, there was an increase in UCP1 expression and preadipocytes in BAT [33]. Fu et al. followed this with an observed increased expression

of vascular endothelial growth-factor A and increased BAT mass mice post exercise [33]. Previous work from our laboratory assessed 14 AT depots in mice, including 5 BAT depots, after 3 weeks of exercise. Exercise affected each depot differently, but interscapular BAT (iBAT) was the tissue most affected by exercise. Gene expression revealed an increase in mitochondrial gene expression in iBAT, but functional data demonstrated a decrease in mitochondrial activity and as well reduced basal glucose uptake [34]. These data suggest that while exercise influences BAT, exercise likely does not increase glucose uptake in BAT in humans or rodents.

It is important to note the fact that exercise does not stimulate glucose uptake in BAT is not surprising; exercise should influence fuel utilization in other tissues such as skeletal muscle and the heart, and any exercise-induced adaptations to BAT would likely influence those tissues. Thus, recent studies have focused on the effects of exercise to mediate the endocrine role of BAT [35], which will be discussed later in this review.

Effects of exercise on white adipose tissue

There are several recent studies that have highlighted the importance of exercise-induced adaptations to WAT [36–38]. In humans, exercise has been shown to increase mitochondrial respiration of scWAT following six weeks of high-intensity exercise [37]. Exercise also improves whole-body glucose metabolism [39], and a previous study showed that a 12-week exercise regime in obese males improved peripheral insulin sensitivity [40]. More recently, a 12-week cycling intervention demonstrated increased expression of brown and beige genes in scWAT, independent of a change in insulin resistance [38]. scWAT is more sensitive to external stimuli and plays a role in insulin sensitivity and regulating the expression and phosphorylation of more than 50% of the glucose uptake genes or proteins [41]. These data demonstrate unique exercise-induced adaptations to glucose homeostasis in scWAT, which can have a distinct impact on whole-body glucose tolerance and insulin sensitivity.

There are several studies identifying exercise-induced changes in WAT in rodents. Unlike humans, a prominent exercise-induced adaptation in rodents is the beiging of scWAT [42]. Mitochondrial genes are also increased in rodents with exercise in both scWAT [43] and vWAT [44], and other studies have also identified exercise-induced changes in scWAT that increase vascular density [45] and expression of genes involved in fatty acid oxidation [34], but these adaptations to scWAT are sex-specific [37]. Previous work from our laboratory has shown that transplantation of scWAT from exercise-trained mice improves skeletal muscle glucose uptake and whole-body insulin sensitivity [46], indicating that scWAT also acts in an endocrine manner to influence cardiometabolic health. These exercise-induced endocrine factors that mediate tissue crosstalk will be discussed in the next section.

Exercise induces secreted factors from adipose tissue that improve cardiovascular health and function

Adipose tissue acts as a major regulator of whole-body homeostasis through intertissue crosstalk via the secretion of adipokines, EVs, and small molecules, which communicate with the heart and skeletal muscle that are in higher energy demands with exercise. These various secreted factors, and how they influence cardiometabolic health, are discussed below.

12,13-Dihydroxy-9Z-octadecanoic acid

12,13-dihydroxy-9Z-octadecanoic acid (12,13-diHOME) is a lipokine released from BAT that has been identified as a molecule to improve cardiac function and overall metabolic health [8,35, 47]. In humans, prolonged bouts of cycling and high-intensity exercise in male athletes increased serum 12,13-diHOME [48], and acute exercise increased plasma 12,13-diHOME in both sedentary and active male and female human subjects [48]. In rodents, Pinckard et al. observed that an acute injection of 12,13-diHOME improved cardiac hemodynamics, and a sustained expression of 12,13-diHOME negated the effects of a high-fat diet on cardiac function [35]. These data identify a direct role for an exercise-induced lipokine from BAT to mediate cardiac function.

Adiponectin

Adiponectin is an adipokine secreted from adipose tissue that is abundant in the blood and alleviates insulin resistance by stimulating lipid oxidation and anti-inflammatory responses [49–51]. Aerobic exercise increases adiponectin in patients who have pre-diabetes or type 2 diabetes [52]. Adiponectin receptors are expressed in cardiomyocytes, and one study found that expression of adiponectin and its receptors was significantly increased after 12 weeks of training at 70% of the heart rate reserve in obese males and females [53]. The increase in adiponectin receptor expression with exercise increased circulating adiponectin levels in females, but not males, suggesting that adiponectin may work in a sex-specific manner. Similarly, another study found that acute aerobic exercise in pre-menopausal females increased circulating adiponectin levels [54]. These data offer insights into potential target pathways via adiponectin receptors to mediate cardiometabolic health.

Fibroblast growth-factor 21

Fibroblast growth factor 21 (FGF21) is mainly expressed in the liver and BAT, with high expression of FGF receptors in adipose tissue [55]. FGF21 has received attention for its role in regulating glucose and lipid

metabolism [56], and studies have found that when FGF21 was replenished, insulin and glucose intolerance was ameliorated [57,58]. In both humans and rodents, studies have indicated that FGF21 was increased after acute exercise bouts of voluntary running wheel, or on a bicycle ergometer or treadmill, respectively [56,59]. Besides the role of FGF21 as a metabolic regulator, it has been indicated to have a protective role in cardiac function.

Ma et al. investigated whether exercise training could increase FGF21 protein expression to alleviate cardiac fibrosis [60]. Mice were given a myocardial infarction (MI) and then underwent a five-week exercise intervention. Both aerobic and resistance training improved cardiac function post training and the authors stated that this was due to the exercise-induced upregulation of FGF21 expression and inhibition of the TGF-β1–Smad2/3–MMP2/9 pathway that ameliorated cardiac fibrosis [60]. Another study found that mice with atherosclerosis treated with exogenous FGF21 had a significant reduction in lipid deposition in the aortic root, with clinical trials finding that FGF21 could predict cardiovascular disease development and improve prognosis [61].

FGF21 inhibits NOD-like receptor protein (NLRP3)-mediated pyroptosis [62], which has been shown to have a pathological influence on cardiovascular diseases [63]. Li et al. observed that aerobic exercise reduced aortic plaque in high-fat diet apolipoprotein E-deficient mice. Importantly, aerobic exercise increased the sensitivity of FGF21 and its serum levels, which had a downstream effect on NLRP3-mediated pyroptosis as those inflammasomes were downregulated in the aorta [62]. These data provide insights into a mechanism through which aerobic exercise prevents atherosclerosis via the regulation of FGF21 and NLRP3-mediated pyroptosis. The studies discussed above highlight the established role FGF21 has in the regulation of metabolism and cardiovascular health, particularly in response to exercise training.

Transforming growth-factor β2

Transforming growth-factor β2 (TGF-β2) is part of the TGF-B family. Previous work has identified TGF-β2 as an adipokine that is secreted from adipose tissue in response to exercise in humans and rodents [64]. While previous transplantation of scWAT from wild-type exercise-trained mice improved whole-body and skeletal muscle glucose metabolism [46], transplantation of exercise-trained scWAT from mice that were deficient in adipose tissue TGF-β2 did not affect glucose tolerance or skeletal muscle glucose uptake, demonstrating the essential role of scWAT–TGF-β2 to mediate glucose uptake [64]. Moreover, when the mice were treated with TGF-β2 acutely, the effects of the high-fat diet were negated, suggesting that TGF-β2 protects against the effects of a high-fat diet on metabolic health. Expression of TGF-β2 was also increased in human adipocytes after exercise [61]. Although the direct effects of TGF-β2 on cardiac function have not been investigated, these data suggest that TGF-β2 is a potential therapeutic to combat obesity and type-2 diabetes.

Extracellular vesicles

EVs are lipid-bound vesicles secreted into the extracellular space that play a role in intertissue communication [65,66]. There are three main subtypes of EVs: exosomes, microvesicles, and apoptotic bodies [67]. EVs are secreted from a wide variety of cells, including adipocytes [68–70] Recent studies have focused on exercise-induced release of EVs and how they could mediate cardiometabolic health [71,72]. The secretion of small EVs from BAT after four weeks of aerobic exercise was cardioprotective by preventing myocardial ischemia/reperfusion injury in the heart [73]. Similarly, high-fat diet (HFD) mice treated with these exosomes that were released from BAT after exercise had improved glucose tolerance and cardiac function [74]. The restoration of cardiac function included improvements in systolic and diastolic function as seen from echocardiography, as well as reduced cardiomyocyte hypertrophy in the HFD mice. These data offer a potential therapeutic target in the shape of EVs as a means to ameliorate cardiometabolic disease, but the mechanism by which EVs act still needs to be explored.

Non-coding RNAs

Within EVs are bioactive molecules, including long noncoding RNAs (lncRNAs), which play a critical role in the cardiovascular system and have emerged as regulators of cell-to-cell communication [75,76], as well as miRNAs, which can be released with exercise and facilitate tissue crosstalk [77]. While a direct role for lncRNAs released from adipose tissue to mediate cardiovascular function has not been elucidated, several studies have identified a role for miRNAs released from adipose tissue to affect the heart. miRNAs are differentially expressed in tissues, and adipocytes are known contributors to exosomal miRNAs [77]. miRNAs play a role in exercise-induced adaptations to the heart. A study observed after three weeks of voluntary wheel running that miRNA-*222* was upregulated in the heart and induced cardiomyocyte growth and proliferation, which mitigated cardiac remodeling post ischemic injury [78]. More recently, Lew et al. found that in mice with diabetes, a moderate– to high-intensity eight-week exercise regime prevented cardiac dysfunction and miRNA dysregulation, suggesting that tissue-specific miRNAs mediate exercise-induced adaptations [79]. Thus, multiple miRNAs, including miRNA-*222* and miR-126, have been identified to be released from adipose tissue in

response to 3–8 weeks of exercise and affect cardiac function [78,79].

Conclusion

Overall, these studies highlight the importance of exercise-induced adaptations to activate inter-organ crosstalk between adipose tissue and the heart. This review discusses the role of adipose tissue in exercise-induced adaptations, with special attention given to the secretory nature of WAT and BAT. The endocrine function of adipose tissue is the driver of inter-tissue communication as a pathway to improve metabolic health and cardiac function. However, the mechanisms behind exercise-induced tissue crosstalk are unknown, which provides avenues for future research. Future studies should explore the effects of age, sex differences, and how different types of exercise affect adipose tissue and its secretory factors.

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Author contributions

J.A.B and K.I.S designed, wrote, and edited the paper.

Conflict of interest statement

The authors have no potential conflicts of interest to disclose.

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Papers of particular interest, published within the period of review, have been highlighted as:
• of special interest.

Data Availability

No data were used for the research described in the article.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest.

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