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REVIEW

# Exercise-induced adaptations to white and brown adipose tissue

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## ABSTRACT

The beneficial effects of exercise on skeletal muscle and the cardiovascular system have long been known. Recent studies have focused on investigating the effects of exercise on adipose tissue and the effects that these exercise-induced adaptations have on overall metabolic health. Examination of exercise-induced adaptations in both white adipose tissue (WAT) and brown adipose tissue (BAT) has revealed marked differences in each tissue with exercise. In WAT, there are changes to both subcutaneous WAT (scWAT) and visceral WAT (vWAT), including decreased adipocyte size and lipid content, increased expression of metabolic genes, altered secretion of adipokines and increased mitochondrial activity. Adaptations specific to scWAT include lipidomic remodeling of phospholipids and, in rodents, the beiging of scWAT. The changes to BAT are less clear: studies evaluating the effect of exercise on the BAT of humans and rodents have revealed contradictory data, making this an important area of current investigation. In this Review, we discuss the exercise-induced changes to WAT and BAT that have been reported by different studies and highlight the current questions in this field.


**KEY WORDS: Adipose tissue, Exercise, Metabolism**

## Introduction

Exercise is an effective tool to combat obesity and type 2 diabetes (Crandall et al., 2008). The effects of exercise on improvements to both skeletal muscle metabolism and cardiovascular health have been well-established (Holloszy and Coyle, 1984; Myers, 2003) and, therefore, more recent studies have examined the role of exercise-induced adaptations to adipose tissue. In the past, adipose tissue was viewed primarily as a tissue involved in energy storage; however, recent investigations have revealed that the physiological role of adipose tissue is more complex and can be affected by many factors, including exercise.

There are three types of adipose tissue: white adipose tissue (WAT), brown adipose tissue (BAT) and beige adipose tissue. WAT is composed of white adipocytes and the stromal vascular fraction, which includes preadipocytes, mesenchymal stem cells and immune cells. White adipocytes have a unilocular fat droplet that contains triglycerides and comprises most of the cell volume. WAT has many functions, including energy storage in the form of lipids, hormone production and secretion, local tissue architecture and morphology, and immune functions (Tran and Kahn, 2010). WAT is located in many different depots throughout the human body and can be broadly subdivided into visceral WAT (vWAT), which is found around internal organs, and subcutaneous WAT (scWAT), which is found primarily around the thigh and buttocks. Visceral WAT is associated with metabolic impairments (Wang et al., 2005; Carey et al., 1997), whereas scWAT has been linked to insulin sensitivity and a reduced risk of type 2 diabetes (Misra et al., 1997; Snijder et al., 2003). The two WAT depots have intrinsically different molecular characteristics that may account for the depot-specific metabolic properties. Among these, vWAT has a higher concentration of androgen receptors, lower levels of leptin secretion and leptin mRNA expression, a higher density of glucocorticoids, and higher levels of IL-6 secretion compared with scWAT (Ibrahim, 2010). These intrinsic depot differences may also play an important role in the effects of exercise on each specific depot.

Similar to humans, rodents have several WAT depots that can be divided into scWAT and vWAT. Rodents have two major scWAT depots: one is located anteriorly between the scapulae; the other scWAT depot, commonly referred to as the inguinal WAT (ingWAT), is located posteriorly, spreading from the dorsolumbar region to the gluteal region (Cinti, 2007). The rodent ingWAT is the most comparable depot to the major scWAT depot in humans in terms of location and, thus, is the most common scWAT depot studied in rodents. Furthermore, like humans, rodents also have several vWAT depots located around their internal organs. The largest and most accessible of these vWAT depots is the perigonadal WAT, making it the most frequently studied vWAT depot in rodents (Chusyd et al., 2016).

BAT is a thermogenic tissue that helps in the regulation of body temperature through non-shivering thermogenesis (Foster and Frydman, 1979) and is composed of multilocular brown adipocytes that have numerous mitochondria and increased expression of the gene encoding the uncoupling protein 1 (UCP1) (Cousin et al., 1992). UCP1 increases proton leakage across the inner mitochondrial membrane and releases the proton motive force as heat rather than driving ATP synthase (Klingenberg, 1990), resulting in a thermogenic effect. Anatomists alluded to the presence of BAT in adult humans in the early 1900s (Bonnot, 1908; Rasmussen, 1922); however, in 2009, three seminal papers confirmed the presence of active BAT in adult humans, leading to an increased focus on this tissue in metabolic research (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009). In adult humans, BAT is found in the neck, supraclavicular and axillary regions, in the paravertebral region, and around major blood vessels, including the aorta and renal arteries (Sacks and Symonds, 2013). The amount of BAT in humans varies with body mass index, age, gender and environmental factors, including outdoor cold exposure (Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Cypess et al., 2009). Although the largest BAT depot in rodents is located in the interscapular region, just as in humans, BAT can also be found in rodents around the neck, mediastinal region, and around major vessels, including the aorta and renal arteries (Cinti, 2007).

The third type of adipose tissue is beige adipose tissue. Beige adipocytes derive from a Myf5– cell lineage, whereas classical brown fat adipocytes originate from a Myf5+ cell lineage (Harms and Seale, 2013). Beige adipocytes are found intermixed within the WAT and appear morphologically similar to brown adipocytes with

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multilocular lipid droplets and an abundance of mitochondria (Hirshman et al., 1989; Enerbäck, 2009; Petrovic et al., 2010; Ishibashi and Seale, 2010). In rodents, beige cells can be induced by a variety of stimuli, including β3-selective adrenergic agonists (Ishibashi and Seale, 2010), cold-exposure (Petrovic et al., 2010), exercise (Stanford et al., 2015a,b; Sutherland et al., 2009; Trevellin et al., 2014; Boström et al., 2012; Cao et al., 2011) and an enriched environment (Cao et al., 2011). Upon stimulation, beige adipocytes express very high levels of Ucp1, show increased fuel oxidation and contribute to non-shivering thermogenesis (Wu et al., 2012; Shabalina et al., 2013). The presence of beige adipocytes in humans has not been studied as extensively as it has in rodents; however, human scWAT has been shown to contain cells that, upon activation, express high levels of UCP1 and other beige markers (Elabd et al., 2009).

## Exercise effects on WAT

Exercise-training, defined as regular bouts of physical activity over a span of weeks, months or years, has well-established effects on adipocyte size (Gollisch et al., 2009; Craig et al., 1981), mitochondrial activity (Stanford et al., 2015a,b; Trevellin et al., 2014; Stallknecht et al., 1991), secretion of adipokines (Golbidi and Laher, 2014; Zachwieja et al., 1997; Bradley et al., 2008; Kraemer et al., 1999; Kanaley et al., 2001) and gene expression (Stanford et al., 2015a,b) in both vWAT and scWAT. There are also specific adaptations to each WAT depot, including adaptations to the structural lipidomic profile changes in scWAT (May et al., 2017) and the beiging of scWAT in rodents (Stanford et al., 2015a,b; Sutherland et al., 2009; Trevellin et al., 2014; Boström et al., 2012; Cao et al., 2011; Stanford and Goodyear, 2016) (Fig. 1).

### Exercise increases mitochondrial activity in both scWAT and vWAT

An exercise-induced increase in mitochondrial activity has been observed in both the vWAT and scWAT of rodents (Stanford et al., 2015a,b; Stallknecht et al., 1991; Vernochet et al., 2012; Wu et al., 2014). Studies examining the effects of swim training over a 4- or 8-week period reported increased cytochrome *c* oxidase activity in vWAT and increased expression of the mitochondrial marker *Pgc1α* in both vWAT and scWAT, indicating an increase in mitochondrial activity (Sutherland et al., 2009; Stallknecht et al., 1991). Investigations on the effects of treadmill exercise on adipose tissue in rats showed that 8 weeks of treadmill training also significantly increased the amount of Pgc1α in the scWAT of the exercise-trained rats (Wu et al., 2014). A study in our laboratory demonstrated an increase in mitochondrial activity in the scWAT of mice after 11 days of voluntary wheel cage running by measuring the oxygen consumption rate and mitochondrial gene expression levels (Stanford et al., 2015a,b). Importantly, these studies demonstrate that a variety of exercise modalities (swimming, treadmill training or voluntary exercise), over varying amounts of time (11 days to 8 weeks) all result in an increase in mitochondrial activity in the WAT of rodents.

An exercise-induced increase in mitochondrial activity in the WAT of humans has also been observed. One study investigated a 6-month mild exercise intervention consisting of 3 h of exercise per week (1 h of spinning on a cycle ergometer and two 1-h sessions of aerobic exercise per week) in healthy, sedentary men. After 6 months of exercise, the expression of genes involved in oxidative phosphorylation was significantly increased in the scWAT of the subjects (Rönn et al., 2014). Another study investigated the effects of an intensive, 4-week exercise intervention (three 1-h sessions of swimming or biking in total/week) in sedentary men and women who had normal glucose tolerance, impaired glucose tolerance or who were type 2 diabetics. Four weeks of exercise training significantly increased the expression of *PGC1α* in the scWAT of these subjects, regardless of gender or pre-exercise glucose tolerance status (Ruschke et al., 2010). Together, these studies consistently demonstrate that exercise training has marked effects on mitochondrial gene expression and activity in human WAT. Importantly, these changes in mitochondrial activity occurred in both rodents and humans, in response to various modalities of exercise, and over various training durations.

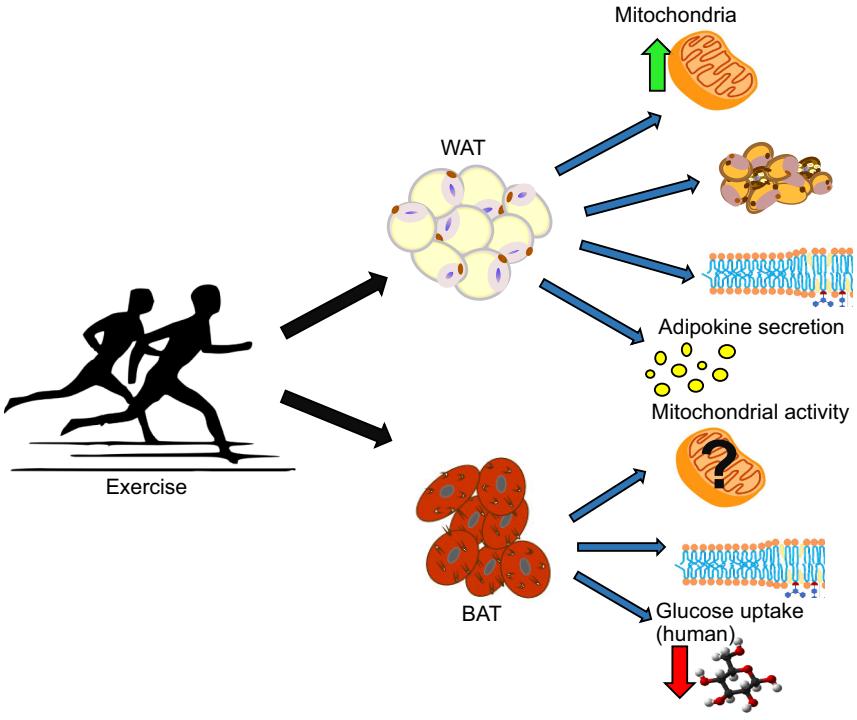


**Fig. 1. Exercise-induced adaptations to white adipose tissue (WAT) and brown adipose tissue (BAT).** Exercise-induced adaptations to WAT include increased mitochondrial activity, beiging of scWAT in rodents, changes to the lipidome and altered adipokine secretion. Exercise-induced adaptations to BAT include changes to mitochondrial activity, adaptations to the lipidome and decreases in glucose uptake in humans.

### Exercise-induced adaptations to WAT improve overall metabolic health

Exercise training alters many characteristics of WAT, including mitochondrial biogenesis, gene expression and adipocyte morphology. Exercise training improves whole-body glucose homeostasis and increases insulin sensitivity (Bonadonna et al., 1993). However, the effects of exercise-induced adaptations to WAT on whole-body metabolic health have not been fully established. Our laboratory addressed this question by transplanting exercise-trained WAT into sedentary mice (Stanford et al., 2015a,b). In this study, 10-week-old mice were either sedentary or exercise-trained in voluntary wheel cages for 11 days. The scWAT and vWAT from both the sedentary and exercise-trained mice were removed and transplanted into age-matched sedentary mice. Nine days post-transplantation, there was a pronounced improvement in the glucose tolerance of mice that had received the exercise-trained scWAT transplant compared with that of mice that received the sedentary scWAT transplant and that of the sham-operated controls (Fig. 2A). Interestingly, there was no difference in glucose tolerance among mice that received sedentary vWAT, exercise-trained vWAT or were sham-operated (Fig. 2B) (Stanford et al., 2015a,b). These data demonstrate that exercise-induced adaptations to scWAT and vWAT in mice are different and have dramatically different effects on overall metabolic health.

After recording the striking improvement in glucose tolerance in mice that received exercise-trained scWAT, these mice underwent further metabolic characterization (Stanford et al., 2015a,b). Mice that received exercise-trained scWAT showed a decrease in fasting blood glucose, insulin and cholesterol concentrations compared with mice that received sedentary scWAT and the sham-operated mice. Insulin tolerance testing also revealed increased peripheral insulin sensitivity in mice that received exercise-trained scWAT compared with that of other groups. Mice transplanted with exercise-trained scWAT showed increased insulin-stimulated glucose uptake in their skeletal muscle and BAT compared with mice that received sedentary scWAT and the sham-operated mice. Taken together, these data indicate that exercise-induced adaptations to scWAT have a beneficial effect on whole-body metabolism, and these improvements occur independently of exercise-induced adaptations to other tissues of influence. Importantly, the beneficial effects of transplanting exercise-trained scWAT diminished rapidly. The improvement in glucose tolerance was not as pronounced at 14 days post-transplantation, and there was only a trend for improved glucose tolerance at day 28. Nevertheless, the novel finding that transplantation of exercise-trained scWAT leads to a short-term systemic improvement in glucose tolerance is important. Future studies will investigate whether the exercise-induced improvements are a result of adipokines secreted from trained scWAT, or a direct effect of transplantation of 'beige' scWAT.

### Exercise alters adipokine secretion

Adipokines are cytokines that are secreted from adipose tissue and act in an autocrine, paracrine or endocrine manner to affect other tissues (Greenberg and Obin, 2006). It is possible that certain beneficial effects of exercise are mediated by an altered adipokine profile (Yamauchi et al., 2002; Singh et al., 2003; Yaspelkis et al., 2004). The two adipokines that have been studied the most, adiponectin and leptin, are significantly affected by exercise and will be the focus of this section. However, there is a myriad of other adipokines (including IL-6 and TNF-α) that are beyond the scope of this Review. Adiponectin plasma levels are inversely correlated with body mass index, vWAT mass and insulin resistance in humans (Mazaki-Tovi et al., 2005). Several studies have investigated the effect of exercise on adiponectin concentration in humans. Although some studies found that the concentration of circulating adiponectin increased after exercise (Lim et al., 2008; Kondo et al., 2006), in other studies, the concentration of circulating adiponectin was unchanged after exercise (Jürimäe et al., 2007; O'Leary et al., 2006; Klimcakova et al., 2006; Nassis et al., 2005; Hara et al., 2005). Likewise, some studies have reported that the concentration of circulating adiponectin in healthy and diabetic rodents increased after exercise (Zeng et al., 2007; Lee et al., 2011), whereas in other studies, the concentration of circulating adiponectin in healthy rodents was unchanged after exercise (Lee et al., 2011; Bhattacharya et al., 2005; Huang et al., 2007).

Leptin is perhaps the adipokine that has been investigated the most. Leptin is released from several tissues, including WAT, BAT, the placenta and the stomach; however, WAT is the principal site of leptin synthesis and secretion and the major determinant of the level of circulating leptin (Trayhurn and Beattie, 2001). Leptin works as a satiety hormone to regulate energy balance through inhibition of hunger. The amount of circulating leptin correlates with adipose tissue mass: a loss of adipose tissue mass in rodents and humans results in decreased serum concentrations of leptin (Zachwieja et al., 1997; Bradley et al., 2008; Kraemer et al., 1999; Kanaley et al., 2001).

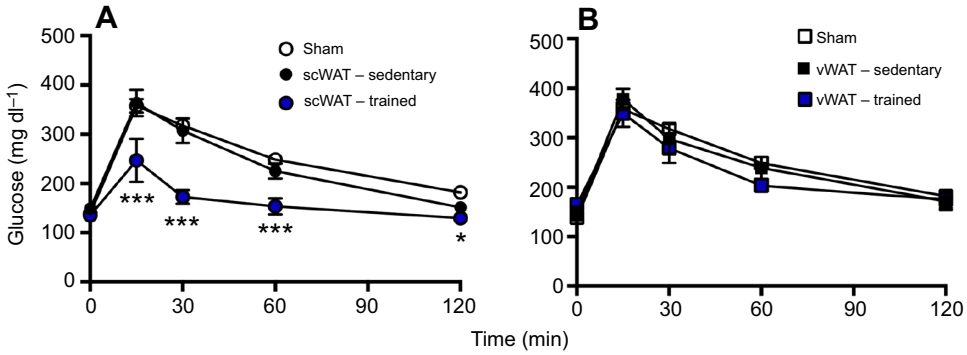


**Fig. 2. Transplantation of trained subcutaneous white adipose tissue (scWAT) improves glucose tolerance.** Mice were transplanted with scWAT (0.85 g) or vWAT (1.0 g) from sedentary or trained mice or were sham operated. For glucose tolerance tests (GTTs), mice were injected with glucose 2 g $kg^{-1}$ body mass i.p. (A) GTT at 9 days post-transplantation for mice transplanted with scWAT and (B) GTT at 9 days post-transplantation for mice transplanted with vWAT. Data are means±s.e.m. ($N$=5–12 per group). *$P$<0.05, ***$P$<0.001. Adapted from Stanford et al. (2015a).

In studies of both lean and obese humans, varying durations of aerobic exercise interventions (4 weeks–1 year) resulted in significant decreases in serum leptin levels; these decreases also correlated with a decrease in fat mass (Yamauchi et al., 2002; Nassis et al., 2005; Sari et al., 2007; Ozcelik et al., 2004; Polak et al., 2006). However, the serum leptin concentration of healthy human subjects was unchanged by resistance exercise (Ara et al., 2006). More investigations are necessary to fully elucidate the role of exercise in the regulation of adipokines.

### Lipidomic changes to scWAT

The rapidly expanding field of lipidomics shows great promise as a means of providing further insight into exercise-induced adaptations to adipose tissue. A recent study in our laboratory investigated the lipidome of scWAT in response to exercise (May et al., 2017). We utilized an MS/MS$^{ALL}$ shotgun lipidomics approach to comprehensively characterize the changes that occurred to the lipidome of scWAT in mice in response to 3 weeks of exercise training. Exercise resulted in a significant decrease in the overall abundance of triacylglycerol (TAG), phosphatidylserines (PS), lysophosphatidylglycerols and lysophosphatidylinositols. There were also numerous decreases in specific molecular species of phosphatidic acid, phosphatidylethanolamines (PE) and PS in scWAT. These changes corresponded with a significant upregulation of several genes involved in phospholipid metabolism (*Agpat3*, *Gpd1*, *Pla2g12a*, *Gpam* and *Ipla2g*). The overall abundance of TAGs was significantly decreased in scWAT, and the genes regulating fatty acid biosynthesis and elongation (*Evol3*, *Evol4*, *Acaca*, *Gpam*, *Agpat3* and *Pparα*) were upregulated with exercise. These data suggest molecular species-specific remodeling of phospholipids and TAGs in scWAT in response to exercise. The decrease in overall TAGs in scWAT, coupled with the upregulation of genes that code for fatty acid biosynthesis and elongation may indicate that the scWAT is working to create a fuel source for the working muscle during exercise (May et al., 2017). Future studies are required to determine the physiological consequences of the exercise-induced changes to the lipidome of scWAT and whether these changes contribute to insulin sensitivity or to other metabolic changes seen with exercise.

## Exercise causes beiging in rodent scWAT

An important exercise-induced adaptation to WAT in rodents is the increase in 'beiging' that occurs in inguinal scWAT. This exercise-induced beiging in inguinal scWAT has been identified in numerous rodent studies investigating the effect of exercise training periods of 11–30 days, including those involving running or swimming (Stanford et al., 2015a,b; Trevellin et al., 2014; Boström et al., 2012; Cao et al., 2011). These beiging adaptations include upregulation of *Ucp1*, *Prdm16*, *Cidea*, *Elov13*, *Pgc1α*, *Pparγ*, *Cox8b*, *Dio2* and otopetrin, as well as increased multilocular cells within the scWAT (Wu et al., 2012).

The unique ability of this phenotypic switch to increase energy expenditure and potentially combat metabolic disease makes the understanding of this mechanism an important topic for investigators. The beiging of scWAT by non-exercise stimuli, including through cold-exposure, environmental factors or pharmaceuticals, is believed to be induced through a heat compensatory mechanism in which adrenergic stimulation compensates for heat loss with the upregulation of UCP1 (Cousin et al., 1992; Cannon and Nedergaard, 2004; Ghorbani and Himms-Hagen, 1997; Ghorbani et al., 1997). However, this mechanism does not make sense in the context of exercise-induced beiging because exercise increases heat production (Saugen and Vøllestad, 1995). Several hypotheses have been proposed as the underlying mechanism (Stanford and Goodyear, 2016), one of which is increased sympathetic innervation, which is known to occur in scWAT during exercise (Nedergaard et al., 2014; Ranallo and Rhodes, 1998). Other hypotheses focus on the exercise-stimulated release of myokines, including irisin (Boström et al., 2012), myostatin (Feldman et al., 2006), meteorin-like 1 (Metrnl) (Rao et al., 2014), lactate (Carriere et al., 2014) and β-aminoisobutyric acid (BAIBA) (Roberts et al., 2014), as well as other secreted factors, including brain-derived neurotrophic factor (BDNF) (Cao et al., 2011). More investigation is needed to fully understand this complex mechanism.

The number of beige adipocytes increases during exercise, which is counterintuitive; exercising skeletal muscles generate heat, so it is unclear why exercise would induce a thermogenic, heat-producing beige adipocyte (Saugen and Vøllestad, 1995). It has been suggested that exercise-induced beiging of scWAT occurs because exercise decreases the adipocyte size and lipid content in scWAT, thus decreasing insulation of the body and necessitating heat production, resulting in the beiging of scWAT (Nedergaard et al., 2014; Stanford and Goodyear, 2016). This hypothesis presents a potential evolutionary significance; it is likely that foraging animals traveling great distances to find food would need a certain amount of plasticity in their adipose tissue to maintain body temperature and, thus, the ability to beige white adipocytes would be evolutionarily advantageous.

Although exercise-induced beiging of scWAT has been well established in rodents, exercise-induced beiging in human scWAT is less clear (Norheim et al., 2014; Vosselman et al., 2015). In a study involving males aged 40–65 years with either normal blood glucose or prediabetic glycemia, a 12-week strength and endurance training program had little effect on the expression of *UCP1* in the scWAT of the subjects, suggesting no change in the thermogenic capacity of the scWAT (Norheim et al., 2014). Other beiging markers (*PRDM16*, *TBX1*, *TMEM26* and *CD137*) were also unaltered in the normal and prediabetic subjects. Another study examined the scWAT of 12 endurance trained athletes and 12 lean sedentary males and found no difference in the mRNA expression of *UCP1* in either the trained or sedentary groups (Vosselman et al., 2015). Although exercise is known to induce significant adaptations to rodent scWAT (Stanford et al., 2015a,b; Trevellin et al., 2014; Boström et al., 2012; Cao et al., 2011), further investigation is required to determine how exercise affects human beige scWAT.

## The curious effects of exercise on BAT

BAT is a thermogenic tissue that is involved in heat production and energy expenditure (Foster and Frydman, 1979). Given that exercise also increases energy expenditure and heat production, it would not be surprising if BAT was downregulated with exercise to maintain body temperature. However, studies investigating the effects of exercise on BAT have yielded conflicting results (Stanford and Goodyear, 2016). In some studies, investigators have shown an increase in mitochondrial activity in rodent BAT (Ignacio et al., 2012; Yoshioka et al., 1989), whereas other studies have revealed a decrease in mitochondrial activity (Wu et al., 2014) and glucose uptake in BAT in exercise-trained humans (Vosselman et al., 2015; Motiani et al., 2017). Exercise has also been shown to affect the composition and concentration of phospholipids and triglycerides in the lipidome of rodent BAT (May et al., 2017).

### Exercise increases BAT mitochondrial activity

To investigate the effects of exercise on BAT activity, young (2-month-old) and old (26-month-old) male mice underwent 6 weeks

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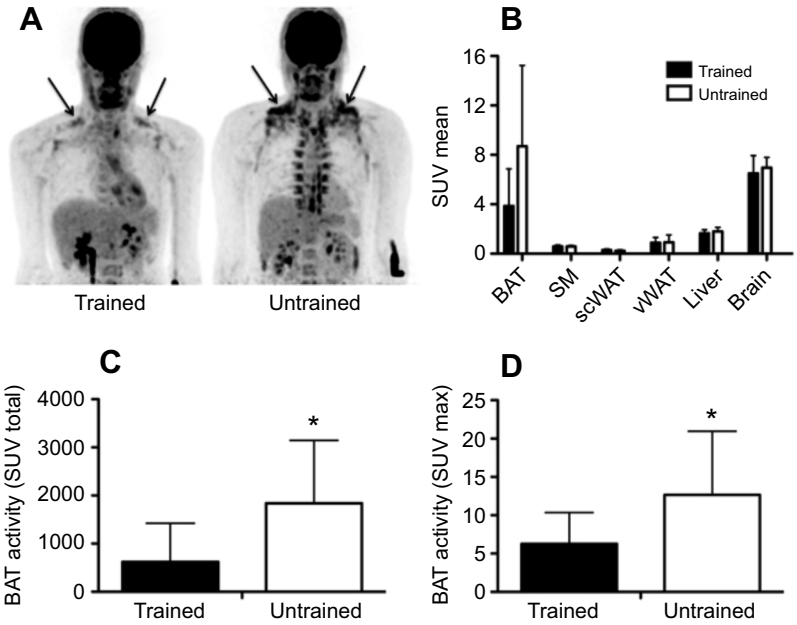


**Fig. 3. Decreased uptake of $^{18}$F-fluorodeoxyglucose ([$^{18}$F]FDG) in brown adipose tissue (BAT) during cold exposure in trained subjects.** (A) Representative [$^{18}$F]FDG-positron emission tomography images demonstrating glucose uptake in trained and untrained test subjects. Black arrows indicate supraclavicular BAT. (B) The average [$^{18}$F]FDG uptake (standardized uptake value, $SUV_{mean}$) measured in multiple tissues in trained and untrained subjects. SM, skeletal muscle; scWAT, subcutaneous white adipose tissue; vWAT, visceral WAT. (C,D) BAT activity, in $SUV_{total}$ (C) and $SUV_{max}$ (D), in trained and untrained subjects. Differences between groups were measured using independent sample *t*-tests. Values are expressed as means±s.d. **P*<0.05. Adapted with permission from Springer Customer Service Centre GmbH [Springer/Nature; International Journal of Obesity, Low brown adipose tissue activity in endurance trained compared to lean sedentary men; M. J. Vosselman, J. Hoeks, B. Brans, H. Pallubinsky, E. B. Nascimento, A. A. van der Lans, E. P. Broeders, F. M. Mottaghy, P. Schrauwen and W. D. van Marken Lichtenbelt (2015)].

of exercise training (swimming) (Oh-ishi et al., 1996). The swim training increased BAT mass and total protein content in BAT in young and old exercise-trained mice. The training also increased the amount of UCP1 antigen in BAT compared with that of the sedentary controls. Other studies examining the effects of 6–8 weeks of swim training in rodents have reported increased blood flow to BAT (Hirata, 1982), increased mitochondrial activity (Ignacio et al., 2012), and increased type 2 deiodinase (dio2) enzymatic activity and mitochondrial respiration in BAT (Ignacio et al., 2012). Rodents that experienced other exercise modalities, including 6–8 weeks of treadmill training, showed an increase in BAT activity: for example, increased cytochrome oxidase activity (Yoshioka et al., 1989), increased oxygen consumption rates (Yoshioka et al., 1989) and upregulation of BAT-specific gene markers (Yoshioka et al., 1989; Xu et al., 2011, 2012). These data suggest that exercise training in rodents can increase mitochondrial biogenesis and activity in BAT.

### Exercise decreases BAT mitochondrial activity and glucose uptake

In contrast to the studies discussed above, more recent studies in rodents and humans have identified a decrease in BAT activity in response to exercise. In a rodent study, 8 weeks of treadmill exercise at 75–85% of $V_{O_2,max}$ for 60 min day$^{-1}$, 5 days week$^{-1}$, resulted in a significant decrease in interscapular BAT mass of 39% compared with that of the sedentary controls (Wu et al., 2014). Ucp1, Pgc1α and fatty acid oxidation were significantly decreased in the BAT of exercise-trained rats.

In humans, two recent studies have investigated the effects of exercise-training on BAT activity. In the first study, 12 lean, sedentary males and 12 endurance-trained athletes aged 18–35 years underwent 2 h of mild cold exposure to investigate cold-induced activation of BAT (Vosselman et al., 2015). BAT activity was measured using $^{18}$F-fluorodeoxyglucose-positron emission tomography-computed tomography ([$^{18}$F]FDG-PET-CT): endurance-trained athletes had significantly decreased cold-stimulated BAT activity compared with that of their lean sedentary counterparts, suggesting that endurance training is linked with lower metabolic activity of BAT in humans (Fig. 3). A second study in humans looked at the effects of short-term exercise training, both high-intensity interval training and moderate-intensity continuous training, on BAT metabolism in sedentary men using 2-[$^{18}$F]flouro-2-deoxy-D-glucose (FDG) and 14(R,S)-[$^{18}$F]fluoro-6-thia-heptadecanoic acid (FTHA) (Motiani et al., 2017). Twenty-eight healthy, middle-aged, sedentary men participated in the study. Basal measures of BAT activity were obtained prior to exercise intervention: subjects with highly active basal BAT had lower body adiposity and leptin concentration, greater whole-body insulin sensitivity and higher high-density lipoprotein cholesterol, suggesting an overall metabolically healthier individual. Exercise training decreased insulin-stimulated glucose uptake in the BAT of subjects who had highly active BAT prior to exercise intervention; however, there was no change in insulin-stimulated glucose uptake in the BAT of subjects who had low active BAT prior to exercise intervention.

In humans, studies investigating the effects of exercise on BAT have only observed a decrease in BAT activity (Vosselman et al., 2015; Motiani et al., 2017). This does not mean that there are no exercise-induced adaptations to BAT; however, these data show exercise decreases cold- or insulin-stimulated glucose uptake in human BAT. This demonstrates that BAT may have different roles in response to exercise in rodents compared with that in humans and that the mechanism by which these exercise adaptations occur may differ between the two species. These varying results between rodents and humans warrant more investigation to determine how BAT responds to exercise and whether it shows potential as a therapeutic remedy to combat metabolic disorders in humans.

### Lipidomic changes to BAT

Recent work in our laboratory investigated the effects of exercise on the BAT lipidome in mice (May et al., 2017). After 3 weeks of voluntary wheel cage running, there was a significant decrease in the abundance of three major lipid classes: TAGs, phosphatidylcholines (PC) and cholesterol esters. Exercise also significantly increased several specific molecular species of PC and PE in BAT. Genes involved in phospholipid metabolism, including *Agpat3*, *Gpd1*, *Lgpat1*, *Ptdss2* and *Pld1*, were significantly downregulated in BAT after exercise. Genes regulating fatty acid biosynthesis, including *Acaca*, *Scd1*, *Agpat3*, *Dgkd* and *Mlxipl*, were significantly

downregulated in BAT, mirroring the decrease in the overall abundance of TAGs in BAT. The physiological mechanism behind these species-specific lipidomic adaptations and the effect on function, glucose tolerance and insulin sensitivity has not been determined and will be the topic of future investigations.

## Conclusions

Several investigations have demonstrated numerous adaptations to WAT and BAT in response to exercise. In WAT, these adaptations include increased mitochondrial biogenesis and gene expression, changes to adipokine secretion, alterations in the lipidome of scWAT and an increased beiging of scWAT in rodents. Exercise-induced adaptations to scWAT also lead to improvements in whole-body metabolic health, supporting the idea that adipose tissue plays an important role as a major endocrine organ that can be stimulated by exercise. In BAT, the effects of exercise are less clear. In rodents, the mitochondrial activity of BAT has been reported to both increase and decrease in response to exercise. In humans, exercise-training decreases cold- and insulin-stimulated glucose uptake in BAT. This may demonstrate that rodent BAT and human BAT respond differently to exercise. More investigation is required to fully understand the impact of exercise-induced adaptations to adipose tissue and their effect on metabolic health. Elucidation of the adaptations to adipose tissue with exercise may ultimately lead to more effective exercise intervention programs and therapeutic remedies aimed at combating the growing epidemic of metabolic diseases.

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### Competing interests

The authors declare no competing or financial interests.

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