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"Weighing" the effects of exercise and intrinsic aerobic capacity: are there beneficial effects independent of changes in weight?

John P. Thyfault[*] and

Molecular and Integrative Physiology, University of Kansas Medical Center, 2067 Hemenway Life Sciences and Innovation Center, MS:3043, 3901 Rainbow Blvd., Kansas, KS 66160, USA; Research Service, Kansas City VA Medical Center, Kansas City, MO 64128, USA

David C. Wright[*]

Department of Human Health and Nutritional Sciences, Room 343 Animal Sciences Building, University of Guelph, Guelph, ON N1G 2W1, Canada

Abstract

It has been known for centuries that regularly performed exercise has beneficial effects on metabolic health. Owing to its central role in locomotion and the fact that it accounts for a large majority of whole-body glucose disposal and fatty acid oxidation, the effects of exercise on skeletal muscle has been a central focus in exercise physiology research. With this being said it is becoming increasingly well recognized that both adipose tissue and liver metabolism are robustly modified by exercise, especially in conditions of obesity and insulin resistance. One of the difficult questions to address is if the effects of exercise are direct or occur secondary to exercise-induced weight loss. The purpose of this review is to highlight recent work that has attempted to tease out the protective effects of exercise, or intrinsic aerobic capacity, against metabolic and inflammatory challenges as it relates to the treatment and prevention of obesity and insulin resistance. Recent studies reporting improvements in liver and adipose tissue insulin action following a single bout of exercise will also be discussed. The research highlighted in this review sheds new insight into protective, anti-inflammatory effects of exercise that occur largely independent of changes in adiposity and body weight.

Keywords

exercise; liver; adipose; insulin; obesity; glucose; inflammation; metabolism; aerobic capacity

Introduction

It has been known for centuries that regularly performed exercise can be an effective tool with which to improve health. In fact, in the sixth century B.C. the Indian physician Susruta advocated exercise as a means to treat diabetes (Tipton 2008). Since these early beginnings the field of exercise physiology, especially as it relates to insulin resistance and diabetes, has

Corresponding author: David C. Wright (dcwright@uoguelph.ca).

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been heavily focused on skeletal muscle. This “muscle-centric” approach makes sense as skeletal muscle is the primary tissue involved in locomotion, is a major site of oxygen consumption during exercise, and serves as a primary sink for the disposal of blood glucose under hyperinsulinemic conditions (DeFronzo 1988). Seminal work in this area has shown that muscle contractions and exercise stimulate increases in skeletal muscle mitochondrial content, oxygen consumption, and glucose uptake (Holloszy and Narahara 1967; Wallberg-Henriksson et al. 1988) and increase the sensitivity of muscle to insulin (Richter et al. 1982). While these noteworthy findings have served as key building blocks in the field, there is a growing appreciation that extra-muscular tissues, such as adipose tissue and liver, are also targeted by exercise and could play an important role in the improved metabolic profile associated with exercise. For example adipose tissue is an active endocrine organ (Rosen and Spiegelman 2006) that is dramatically influenced by exercise (Thompson et al. 2012). The importance of adipose tissue in regulating training-induced changes in glucose homeostasis has been recently highlighted by work demonstrating that the transplantation of adipose tissue from trained mice into obese, insulin-resistant animals leads to improvements in glucose homeostasis (Stanford et al. 2015). Similarly, the liver also appears toplay an important role in mediating the beneficial effects of exercise. In individuals with nonalcoholic fatty liver disease exercise can lead to rapid decreases in markers of liver damage that parallel improvements in insulin sensitivity (Fealy et al. 2012). Given these points the purpose of the current review is to highlight the effects of exercise and intrinsic aerobic capacity on adipose tissue and liver metabolism as it relates to the treatment and prevention of obesity, insulin resistance, and inflammation. A particular focus of this paper will be centered upon teasing out the effects of exercise, or aerobic capacity, independent of changes in adiposity, on the regulation of adipose tissue and liver metabolism.

Is there a protective effect of exercise training independent of weight loss?

Adipose tissue

Obesity, which is caused to a large extent by physical inactivity and over-nutrition, is associated with a myriad of harmful conditions such as cancer (Khandekar et al. 2011), type 2 diabetes (Kahn et al. 2006), cardiovascular disease (Nakamura et al. 2014), hepatic steatosis (Masuoka and Chalasani 2013) and neuro-degeneration (Hildreth et al. 2012). A central event linking obesity to these comorbidities is the development of insulin resistance. Although the pathogenesis of insulin resistance has not been fully delineated, there is a growing appreciation that inflammation is a central event in this process. This possibility was first documented over a century ago when it was reported that the anti-inflammatory drug, salicylate, improved symptoms of diabetes (Williamson 1901). Some 90 years later Hotamisligil et al. (1993) found that the messenger RNA (mRNA) expression of the pro-inflammatory cytokine tumour necrosis factor alpha (TNFα) was elevated in adipose tissue from obese, insulin-resistant rodents and that the neutralization of TNFα improved whole-body glucose homeostasis. These ground-breaking findings, and many investigations since (Sabio et al. 2008; Saberi et al. 2009; Stienstra et al. 2011; Wiedemann et al. 2013) have provided strong evidence that inflammation is a causal player in the pathogenesis of insulin resistance. With this being said, it should be noted, however, that alterations in adipose tissue

inflammation are not always associated with parallel changes in insulin sensitivity (Kraakman et al. 2015).

Given the purported role of inflammation in regulating glucose homeostasis, it is of great interest to identify and optimize interventions that can be used to protect against and treat inflammation. In this vein exercise has long been recognized as an effective lifestyle approach with which to reduce chronic inflammation. Observational data from several large population cohort studies have demonstrated an inverse relationship between physical activity levels and markers of inflammation (Geffken et al. 2001; Abramson and Vaccarino 2002; Wannamethee et al. 2002). That is, individuals who reported performing more frequent and intense physical activity displayed lower levels of systemic inflammation. However, data from human intervention studies are mixed, with the greatest beneficial effects of exercise seen in individuals with the highest levels of circulating inflammatory markers at the onset of training (as reviewed in Beavers et al. (2010)). At the tissue level, a 15-week lifestyle intervention consisting of exercise training and a hypo-caloric diet reduced markers of macrophage infiltration and pro-inflammatory gene expression in adipose tissue from obese humans (Bruun et al. 2006). However, in this study the subjects lost a considerable amount of weight (~18 kg), thus making it difficult to tease out the relative contribution of exercise per se versus weight loss. In a subsequent investigation comparing the effects of exercise and diet-induced weight loss, circulating inflammatory markers were reduced to a much greater extent with diet-induced weight loss than with exercise training, with those losing the greatest amount of weight experiencing the largest reductions in circulating inflammatory markers (Christiansen et al. 2010). The association between weight loss and the anti-inflammatory effects of exercise training has also been demonstrated in rodent-based studies. For example, in conditions of pre-existing obesity, exercise training reduces the expression of inflammatory markers in adipose tissue in parallel with reductions in fat pad mass (Vieira et al. 2009a, 2009b). Similarly, initiating exercise training at the onset of a high-fat diet prevents weight gain, macrophage infiltration, and the increase in expression of inflammatory markers in mouse adipose tissue (Baynard et al. 2012; Yan et al. 2012). In lean, healthy mice that do not display increases in inflammatory markers, exercise training has negligible effects on the expression of pro-inflammatory cytokines in adipose tissue (Baynard et al. 2012). Taken together these findings provide evidence that the beneficial effects of exercise training on inflammation are largely dependent on either the prevention of weight gain or, in conditions of pre-existing obesity and inflammation, the induction of weight loss.

At first glance, the above-mentioned data would question the utility of exercise training as an effective means with which to modulate adipose tissue inflammation independent of its effects on preventing and/or reversing obesity. However, what is not clear is if aerobic exercise training would alter adipose tissue immuno-metabolism in such a way as to confer a protective effect in the face of an inflammatory insult. In other words, would trained individuals be better able to withstand an acute inflammatory challenge? This is an important question to answer given the rapidity with which inflammation develops and its purported casual role in the etiology of insulin resistance (Wiedemann et al. 2013). Over the past several years we have been examining this question using a variety of different inflammatory insults. We reasoned, based on the previously mentioned studies, that exercise

training would not lead to obvious changes in the metabolic and inflammatory profile of lean, healthy animals. However, when presented with metabolic or inflammatory insults we surmised that noticeable differences with training would be uncovered. As an initial test of this hypothesis we used the pharmacological agent CL 316 243 (CL). CL is a specific beta 3 adrenergic agonist that when injected into rodents causes a large induction of pro-inflammatory genes in adipose tissue (Roth Flach et al. 2013). The induction of inflammation with CL is likely linked to increases in adipose tissue lipolysis and fatty acid release. Evidence for this comes from experiments in which CL-mediated increases in markers of adipose tissue inflammation were attenuated when lipolysis was pharmacologically blocked (Mottillo et al. 2010). In our study, mice were exercise trained for 4 weeks and were then treated with CL or an equivalent volume of saline for 2 days after the last bout of exercise and tissues were harvested at 4 h post-injection. In saline-treated mice there were no detectable differences in markers of adipose tissue inflammation between sedentary and trained mice. However, when presented with an inflammatory insult, previously trained mice displayed an attenuated increase in pro-inflammatory genes such as TNFα (Castellani et al. 2014).

From a mechanistic perspective the attenuated response to CL in trained mice did not appear to be secondary to differences in lipolysis as CL-induced increases in plasma fatty acids and glycerol were similar between sedentary and trained mice. Moreover, CL-induced increases in the phosphorylation of hormone-sensitive lipase and extracelluar regulated kinase, enzymes that are involved in lipolysis (Greenberg et al. 2001; Haemmerle et al. 2002), were comparable in adipose tissue from trained and sedentary mice. Recent work has demonstrated that the membrane associated calcium channel transient receptor potential vanilloid 4 (TRPV4) regulates adipocyte inflammation (Ye et al. 2012). The knockdown of TRPV4 in 3T3 adipocytes led to reductions in the expression of a wide range of pro-inflammatory genes. Similarly, TRPV4-deficient mice, or mice treated with a TRPV4 antagonist, are protected against high-fat diet–induced glucose intolerance and displayed reductions in markers of adipose tissue inflammation (Ye et al. 2012). Although only demonstrating an associative relationship, we found that TRPV4 protein content was reduced in epididymal adipose tissue from trained compared with sedentary mice, providing evidence that this could be a potential mechanism through which training protects against adipose tissue inflammation.

Liver

Based on the above findings we were further interested in determining if tissues besides adipose were also protected against inflammatory stressors following training. To examine this question we used a model of habitual physical activity in which mice were provided with running wheels in their cages for ~2.5 months. During the course of the study mice ran ~4–5 km/day and at the end of the intervention were lighter and displayed greater glucose tolerance than sedentary animals (Peppler et al. 2016). We then challenged mice with lipopolysaccharide (LPS), a component of gram-negative bacteria, which is used to experimentally induce severe inflammation and sepsis in experimental animals (Schertzer et al. 2011). As with our previous study, differences in indices of inflammation in the absence of inflammatory stimuli were subtle. However, increases in markers of liver and systemic

inflammation were attenuated in habitually active mice, and this was associated with slight reductions in LPS-induced insulin resistance (Peppler et al. 2016). These findings are consistent with recent work demonstrating that LPS-induced inflammation was reduced in subcutaneous adipose tissue biopsies from trained compared with untrained subjects (Olesen et al. 2015) and blunted increases in cytokine secretion in human whole-blood cultures following training (Timmerman et al. 2008).

Are animals with high intrinsic aerobic capacity protected against metabolic insults?

Low- (LCR) and high-capacity runners (HCR)

Low aerobic capacity is a predictor of cardiovascular disease and all-cause mortality, whereas both maintaining and improving aerobic capacity increases survival in previously low-fitness individuals (Kodama et al. 2009; Kokkinos et al. 2010). A useful model to study the protective role of intrinsic aerobic capacity was developed by Britton and Koch, in which they selectively bred rats for low- or high-endurance running capacity, resulting in HCR and LCR. After 11 generations of selective breeding, the rats in the LCR group ran approximately 200 m before reaching exhaustion on a treadmill test while the HCR ran nearly 2000 m before exhaustion, a 10-fold difference (Wisloff et al. 2005). Indirect calorimetry measured during maximal treadmill testing revealed that peak oxygen consumption is ~30 mL/(kg•min)$^{-1}$ higher in HCR compared with LCR rats (Torma et al. 2014). Thus, both endurance running capacity and maximal rates of oxygen consumption were dramatically different because of breeding for running capacity. Importantly, these differences in running capacity are intrinsic as the rats do not have access to wheels or treadmills and are only maintained in home-cage settings. In addition, the HCR and LCR display traits that uniquely model low and high-fitness human subjects, including that the LCR display obesity, cardiovascular risk factors, and fatty liver at a relatively young age (20–30 weeks) on a normal chow diet (Thyfault et al. 2009), display earlier mortality (~6 months) (Koch et al. 2011) than high-fitness HCR rats, and are more susceptible to a variety of disease conditions (as reviewed in Garton et al. (2016)). Britton and Koch have continued to breed the HCR and LCR over 30 generations and information related to running capacity and genetics are reported elsewhere (Koch et al. 2013; Ren et al. 2013).

Intrinsic aerobic capacity and short-term high-fat diets

Similar to the protective effects we reported with prior exercise training (Castellani et al. 2014; Peppler et al. 2016), sedentary but high-fitness HCR rats are protected against chronic metabolic insults while the LCR rats are extremely susceptible (Noland et al. 2007; Naples et al. 2010). In these studies both male (Noland et al. 2007) and female (Naples et al. 2010) HCR rats were protected against high-fat diet–induced weight gain and insulin resistance while the LCR displayed an expected susceptibility. Although these initial investigations provide intriguing insight into the protective effects of intrinsic aerobic capacity, the chronic nature of the feeding intervention allows for a period of homeostasis to occur, making it difficult to examine the acute adaptations to nutrient excess. To examine adaptations to an acute metabolic insult, Morris et al. (2014) fed LCR and HCR rats a low- or high-fat diet

(45%) for 3 days and found that hepatic steatosis (liver triacylglycerol accumulation) significantly increased in the LCR rat while the HCR displayed no change compared with the control low-fat diet. Resting energy expenditure, when adjusted for body weight, fat mass, and fat free mass, was increased in HCR compared with LCR rats on both low- and high-fat diets (Morris et al. 2014). In addition, the HCR rats displayed a greater capacity to switch from a low-fat to a high-fat diet compared with the LCR. That is the HCR rats displayed both a greater drop in RQfrom and a bigger increase in dietary fatty acid oxidation (measured by radiolabeled fatty acids in food tracked to expired CO_2) than the LCR rats after switching from the low- to the high-fat diet. Fatty acid oxidation in liver homogenate and in isolated liver mitochondria was also higher in the HCR than the LCR, suggesting that overall capacity to metabolize lipids at the whole-body level and in the liver likely also played a role in the protection observed in HCR rats. Morris et al. also showed that selective over-expression of hepatic proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) with adenovirus, and a subsequent increase in liver fatty acid oxidation, protected against high-fat diet–induced changes in whole-body metabolic flexibility, further substantiating the critical role of hepatic fat oxidation in impacting whole-body metabolism (Morris et al. 2012).

Intrinsic aerobic capacity and ovariectomy-induced metabolic dysfunction

A protective effect of high-intrinsic aerobic capacity has also been found against ovariectomy-associated obesity and metabolic dysfunction. Specifically, female HCR rats did not exhibit increases in percentage body fat or homeostasis model assessment of insulin resistance, an index of whole-body insulin resistance, compared with LCR rats following the surgical removal of the ovaries (Vieira-Potter et al. 2015). As in this group's previous work (Morris et al. 2014), the protective effects of high-intrinsic aerobic capacity were associated with increases in resting energy expenditure and physical activity in the HCR rats. While these findings provide intriguing evidence of a protective effect of high-intrinsic aerobic capacity against metabolic insults, it is difficult to tease out a specific mechanism that is mediating these effects. Is there something unique about individuals with high-intrinsic aerobic capacity that confers protection against metabolic insults or are the findings generated from this model simply explained by increases in physical activity? A further examination of the results from Morris et al. (2014) show that the higher energy expenditure in the HCR rats is not solely due to greater physical activity. Indirect calorimetry allows for measurements of total energy expenditure (all time points) and resting energy expenditure (when animals are resting and oxygen consumption is at the lowest level). In caged rats, resting energy expenditure makes up ~70% of total energy expenditure. Importantly, the HCR display an ~20%–30% higher resting energy expenditure than the LCR rats, suggesting that greater physical activity does not drive the energy expenditure phenotype.

Does acute exercise reduce inflammation and improve glucose homeostasis?

Studying how animals that have been previously exercise trained or that possess high-intrinsic aerobic capacity respond to nutrient and inflammatory challenges has provided new insights into the beneficial protective effects of aerobic capacity and physical activity.

However, the interpretation of these results is still somewhat difficult as prior training leads to a slight prevention of weight gain, though no apparent differences in inflammatory markers in the unstimulated condition, whereas differences in high-fat diet–induced weight gain are apparent between LCR and HCR rats even after very short feeding interventions. One approach to avoid this issue, and to tease out the direct effects of exercise, is to examine the acute effects of exercise in obese, insulin-resistant animals, as differences in adiposity and/or body weight following a single session of exercise would not be observed. In human clinical studies, improvements in glucose homeostasis with short-term exercise training have been demonstrated independent of weight loss (Thyfault 2008). Similarly swim exercise has been reported to improve insulin action in adipose tissue (Oliveira et al. 2013) and liver (Ropelle et al. 2009) from obese, insulin-resistant rats. While forced swim exercise is stressful and has little clinical significance, similar results have been reported with treadmill exercise. MacPherson et al. (2015) reported that a single bout of treadmill running almost completely rescued high-fat diet–induced insulin resistance in inguinal subcutaneous mouse adipose tissue. Rapid improvements in adipose tissue insulin action with exercise are associated with a shift in macrophage polarization. Oliveira et al. (2013) found that acute swim exercise led to reductions in markers of M1, pro-inflammatory macrophages, and increases in anti-inflammatory M2 macrophages in adipose tissue from rats fed a high-fat diet. Consistent with these findings, MacPherson et al. (2015) reported reductions in indices of M1 macrophages, via quantitative polymerase chain reaction and immunofluorescence, in inguinal subcutaneous adipose tissue from mice fed a high-fat diet following a single bout of treadmill running.

Is there a common mechanism that explains the protective effects of prior exercise training and acute exercise?

Whether it is adipose tissue or liver an important question that arises from our recent studies relates to the signal(s) activated during exercise that lead to the protective effect against subsequent inflammatory insults. Hormesis refers to the concept that “A process in which a low dose of a chemical agent or environmental factor that is damaging at high doses induces an adaptive beneficial effect on the cell or organism” (Mattson 2008). In regards to the currently discussed work it is tempting to speculate that repeated and transient spikes in inflammation with each bout of exercise/activity could serve as signal to turn on pathways that would mitigate subsequent inflammatory challenges. In fact there is some evidence, at least in skeletal muscle, to suggest that this might be the case. In humans, supplementation with resveratrol, a polyphenol compound that possesses anti-inflammatory properties (as reviewed in Liu et al. (2015)), prevents the induction of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1 alpha) in skeletal muscle following 4 weeks of low-volume, high-intensity interval training (Scribbans et al. 2014). Similarly, ibuprofen attenuates increases in skeletal muscle protein fractional synthesis rate following a single bout of eccentric resistance exercise (Trappe et al. 2002). In both adipose tissue (Rosa et al. 2011) and liver (Hoene and Weigert 2010) exercise has been shown to acutely increase markers of inflammation. However, at least in the case of adipose tissue, this would appear to be intensity-dependent as markers of inflammation are robustly increased in rat adipose following an exhaustive bout of treadmill exercise (Rosa et al. 2011), whereas moderate-

intensity exercise induces interleukin (IL)-6 but independent of classically recognized inflammatory markers (i.e., TNFα) in mouse epididymal adipose tissue (Castellani et al. 2015).

While IL-6 has traditionally been viewed as a pro-inflammatory cytokine, there is mounting evidence to suggest that it could possess anti-inflammatory properties. For example, the myeloid specific deletion of the alpha subunit of the IL-6 receptor leads to a worsening of adipose tissue inflammation in mice fed a high-fat diet (Mauer et al. 2014), and inflammation is increased in livers from whole-body IL-6 deficient compared with wild-type mice fed a high-fat diet (Matthews et al. 2010). Given the increases in IL-6 normally reported in conditions of obesity and insulin resistance (see Kraakman et al. (2013) for an excellent review), these findings would perhaps suggest that IL-6 is increased as a consequence of inflammation in an attempt to mitigate or resolve this condition. From the standpoint of exercise, it is tempting to speculate that the acute increases in inflammation with higher intensities of exercise could serve as a signal to induce IL-6. It should be noted, however, that adipose tissue IL-6 signaling can be activated in the absence of inflammation (Castellani et al. 2015) and thus the hormesis argument put forward may not hold in all conditions. Regardless of the triggering signal(s), repeated increases in IL-6 with each bout of exercise could condition the tissue to be better able to withstand subsequent inflammatory challenges.

Similar to exercise training, there is associative evidence to suggest that the improvements in adipose tissue insulin signaling and inflammatory profile with acute exercise in obese rodents could be linked to increases in adipose tissue IL-6 signaling. In support of this, IL-6 mRNA expression and markers of IL-6 signaling such as SOCS3 (suppressor of cytokine signaling 3) mRNA and signal transducer and activator of transcription 3 phosphorylation are increased in parallel with reductions in M1 macrophages and increases in insulin-stimulated Akt phosphorylation in inguinal adipose tissue from obese mice (MacPherson et al. 2015). In contrast to higher intensity exercise in lean, healthy animals, the induction of IL-6 signaling with exercise in adipose tissue from obese mice occurs independent of increases in classically identified markers of inflammation such as TNFα and c-Jun N-terminal kinase phosphorylation. These findings, while demonstrating that the triggering signal inducing IL-6 expression in adipose could be different in lean and obese animals, both point towards potential beneficial effects of IL-6 in modulating adipose tissue metabolism.

If in fact IL-6 serves as a mechanism to reduce adipose tissue inflammation in the setting of obesity, and to protect against acute inflammatory challenges with exercise training, an important question relates to the source of IL-6. Many studies, in both rodents (Ellingsgaard et al. 2011; O'Neill et al. 2013) and humans (Ostrowski et al. 1998; Holmes et al. 2004) have shown that circulating IL-6 levels increase with exercise. The current dogma is that the increase in circulating IL-6 with exercise is muscle derived and signals to adipose tissue and liver (as reviewed in Febbraio and Pedersen (2002)). However, a relatively unappreciated fact is that exercise also increases IL-6 secretion from adipose tissue (Lyngso et al. 2002). At least in humans, the interstitial concentration of IL-6 surrounding adipose tissue is many times higher (ng/mL) than that found in the circulation, even after very strenuous exercise.

Therefore, it is not clear if the increase in adipose tissue IL-6 signaling with exercise is the result of increases in circulating IL-6 or autocrine/paracrine effects of adipose-derived IL-6.

Conclusions

The current review has highlighted recent findings demonstrating protective effects of both exercise training, and intrinsic aerobic capacity, against inflammatory and metabolic insults and has also discussed the powerful effects of a single bout of exercise in rescuing adipose tissue and liver insulin action in obese rodents. Especially in the case of prior training and acute exercise, the protective effect against inflammatory challenges seems to be mediated to a large extent independent of significant differences in adiposityor body weight and suggesta novel anti-inflammatory effect of exercise. Moving forward there are a number of important questions that need to be answered including but not limited to: (*i*) What signals are activated during exercise that lead to the protection against inflammatory insults? (*ii*) Following exercise training how long do the protective effects of exercise persist? (*iii*) What mechanisms contribute to the increase in resting energy expenditure and by extension protection against high-fat diet–induced weight gain in rats with high-intrinsic aerobic capacity? (*iv*) What factors are responsible for the improvement in adipose tissue insulin action and switch in macrophage polarization that occurs following a single bout of exercise in obese, insulin-resistant rodents? Drilling down on these questions will provide important new insights into the beneficial effects of exercise in protecting against and treating derangements in whole-body and tissue-specific indices of immuno-metabolism.

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