

Exercise-Induced Alterations in Muscle Lipid Metabolism Improve Insulin Sensitivity

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HOROWITZ, J.F. Exercise-induced alterations in muscle lipid metabolism improve insulin sensitivity. *Exerc. Sport Sci. Rev.*, Vol. 35, No. 4, pp. 192–196, 2007. *Exercise is a key component for the successful management of many obesity-related metabolic complications, including insulin resistance. This review addresses the effect of chronic and acute endurance exercise on insulin action in obesity and the role of exercise-induced alterations in fatty acid partitioning within the muscle cell on insulin sensitivity.*

Key Words: obesity, type 2 diabetes, exercise training, acute exercise, insulin resistance

INTRODUCTION

Exercise is a cornerstone treatment for obesity-related metabolic complications, including impaired skeletal muscle insulin sensitivity (*i.e.*, reduced ability to increase glucose uptake in response to insulin). However, the mechanisms responsible for the exercise-induced improvement in insulin sensitivity and how much exercise is necessary for this improvement are not completely understood. Excessive fatty acid availability in obesity impairs insulin sensitivity, and the “partitioning” of these fatty acids within the myocyte toward accumulation of intracellular fatty acid intermediates (*e.g.*, ceramide, diacylglyceride (DAG), and long-chain fatty acyl-coenzyme A (CoA)) can mediate this response (Fig. 1). Recently, much emphasis has been placed on the importance of mitochondrial oxidative capacity in the regulation of insulin sensitivity. However, the direct effect of an increased *in vivo* oxidative capacity from endurance exercise training on insulin sensitivity is unclear. Alternatively, it is well established that a single session of exercise can increase insulin sensitivity for hours and even days, but whether an alteration in fatty acid partitioning within muscle contributes to this improvement remains uncertain. Based on our work (18,20), we hypothesize that the fatty acids entering the muscle cell after exercise are preferentially partitioned toward synthesis of triglyceride (which are largely considered inert) rather than toward the production and accumulation of the more damaging fatty

acid intermediates that are known to impair insulin sensitivity. This review addresses the effects of fatty acid partitioning on the regulation of insulin sensitivity, the effects of chronic and acute endurance exercise on insulin action in obesity, and the putative effects of exercise-induced alterations in fatty acid partitioning within the muscle cell on insulin sensitivity.

EXCESSIVE FATTY ACID AVAILABILITY IS AN IMPORTANT MEDIATOR OF INSULIN RESISTANCE

The very high lipolytic rates found in abdominal obesity and the resultant oversupply of systemic fatty acids are important links between obesity and the development of a constellation of obesity-related metabolic complications, including impaired insulin sensitivity. The uptake and subsequent metabolic fate of the excessive fatty acids in skeletal muscle are ultimately responsible for fatty acid-induced changes in muscle insulin action. In obesity, fatty acid oxidation within resting skeletal muscle is not nearly sufficient to meet the very high rates of fatty acid uptake. This “mismatch” between high rates of fatty acid uptake and subsequent metabolism can result in an accumulation of fatty acid intermediates within the muscle cell (*e.g.*, ceramide, diacylglyceride (DAG), and long-chain fatty acyl CoA). In turn, these fatty acid intermediates have been found to induce insulin resistance (9). Much of the inhibitory effect of the fatty acid intermediates work through activation of proinflammatory/stress pathways within skeletal muscle that are known to impair insulin signaling (21). This proinflammatory response involves activation of serine kinases, such as novel protein kinase C (PKC), *c-Jun N-terminal kinase* (JNK), and inhibitor- κ B kinase/nuclear factor- κ B (I κ B/NF- κ B), which suppress insulin action (21) (Fig. 2). Activation of these proinflammatory pathways is elevated in obesity perhaps largely because

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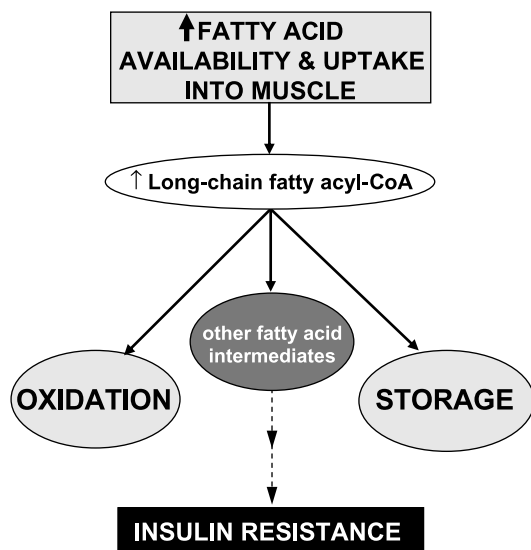


Figure 1. Schematic diagram outlining the primary metabolic fates of fatty acids in skeletal muscle: oxidation, storage (as intramyocellular triglyceride (IMTG)), and formation/accumulation of fatty acid intermediates (e.g., ceramide, diacylglyceride (DAG), and long-chain fatty acyl-CoA). Accumulation of these fatty acid intermediates can ultimately induce insulin resistance.

of the excessive fatty acid availability. Therefore, improving the mismatch between fatty acid flux into skeletal muscle and the subsequent “metabolism” of these fatty acids may improve insulin sensitivity via a reversal in the activation of one or all of these proinflammatory/stress pathways.

FATTY ACID METABOLISM AND INSULIN SENSITIVITY AFTER ENDURANCE TRAINING

Insulin sensitivity is often reported to increase after endurance exercise training, but many issues confound the elucidation of the putative mechanisms involved in this response. One way to reduce the mismatch between fatty acid uptake and subsequent metabolism in skeletal muscle (and thereby reduce the accumulation of fatty acid intermediates) is to reduce fatty acid availability by suppressing the rate of lipolysis. However, we and several others have demonstrated that endurance exercise training, without weight loss, does not affect lipolytic rate after an overnight fast. We have also demonstrated that endurance exercise training does not affect lipolytic sensitivity to epinephrine (10) or lipolytic rate during exercise (11), as long as body weight and body composition are the same before and after training. In contrast to these findings, Friedlander *et al.* (6), reported that training actually increased lipolytic rate. However, Friedlander *et al.* (6) measured lipolysis in the postprandial state. Because insulin is an extremely potent and persistent inhibitor of lipolysis and because endurance training typically reduces the insulin response to a meal, a lower insulin response to the meal after training likely impacted their results.

Alternatively, training-induced alterations in fatty acid oxidation have been suggested to play an important role in regulating insulin sensitivity. Several recent reports suggest that low mitochondrial oxidative capacity may be a key determinant in the development of insulin resistance (15).

It has been postulated that a limited capacity for oxidative disposal of fatty acids may increase the formation and accumulation of intracellular fatty acid intermediates that can disrupt insulin signaling (21). Therefore, because increased oxidative capacity is a classic adaptation to endurance training, it seems very reasonable to hypothesize that a training-induced increase in oxidative capacity may enhance insulin sensitivity. However, although endurance exercise training is commonly found to increase fatty acid oxidation during exercise, an increase in resting fatty acid oxidation after training is not as robust. It is also important to note that even when endurance training is found to induce a measurable increase in resting fatty acid oxidation, the typical magnitude of this increase (*i.e.*, 10–20 $\mu\text{mol}\cdot\text{min}^{-1}$) is very small in comparison to the rate of fatty acid mobilization in abdominal obesity (*i.e.*, 400–600 $\mu\text{mol}\cdot\text{min}^{-1}$). We recently reported that adding endurance exercise training to a weight loss intervention increased resting whole body fatty acid oxidation by approximately 25%, whereas weight loss without exercise training had no effect on fat oxidation (19). However, we subsequently found the improvement in insulin sensitivity to be no different between these groups. Additionally, although previous reports indicate that insulin-resistant offspring of patients with type 2 diabetes have low oxidative capacity (15), it has recently been found that offspring of patients with type 2 diabetes increased oxidative capacity with exercise training similarly as healthy control subjects. Importantly, it was found that the increase in oxidative capacity after exercise training in the offspring of patients with type 2 diabetes was not associated with an improvement in insulin sensitivity, suggesting that their low oxidative capacity may not explain their impaired insulin sensitivity (14). Moreover, it has been demonstrated that endurance training without weight loss did not improve insulin sensitivity, despite marked increases in oxidative capacity (17). It is important to recognize that having an increased capacity to oxidize fatty acids does not necessarily equate to a meaningful increase in fatty acid oxidation at rest, in part because resting energy expenditure is very low. Therefore, even if fatty acid oxidative capacity is elevated, this may

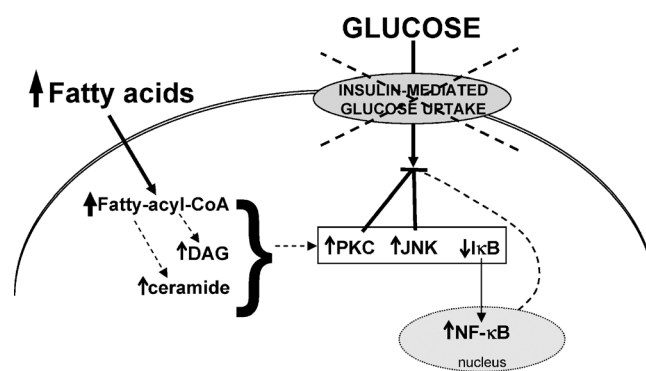


Figure 2. Hypothetical scheme to explain the effect of elevated concentration of fatty acid intermediates (e.g., fatty acyl-CoA, ceramide, and DAG) in skeletal muscle on the activation of markers for proinflammatory pathways (e.g., protein kinase C (PKC), c-Jun *N*-terminal kinase (JNK), and inhibitor- κ B kinase/nuclear factor- κ B (I κ B/NF- κ B)) and the subsequent reduction in insulin-mediated glucose uptake.

do little to compensate for excessive fatty acid availability and uptake found in obesity.

INSULIN-SENSITIZING EFFECTS OF EXERCISE TRAINING OFTEN FOUND TO BE SHORT LIVED

Additional evidence supporting the notion that a training-induced increase in oxidative capacity may not provide a robust increase in insulin sensitivity is that the improvement in insulin sensitivity after several weeks, months, and even years of endurance exercise training are often found to return to near untrained levels even after just a few days without exercise (4) (Fig. 3), despite a persistent increase in oxidative capacity. It must be acknowledged that the concept that endurance exercise training, *per se*, provides little if any persistent improvement in insulin sensitivity is not universal. Many studies report improved insulin sensitivity after endurance training. However, many of these studies tested their subject 24–48 h after the last training session, which confounds the interpretation because of the profound effect of acute exercise on insulin sensitivity (discussed below). There are studies that report a persistent increase in insulin sensitivity after three or more days without exercise, which should be long enough to remove much of the influence of the last training session. The reason for this discrepancy remains unclear, but it is important to note that changes in muscle glycogen concentration (3), energy balance (1), and body weight (1) can greatly influence insulin sensitivity, and controlling for these factors during/after an exercise training program can be very challenging. This may help explain much of the discrepancy in studies that report improved insulin sensitivity after training.

IMPROVEMENT IN INSULIN SENSITIVITY AFTER ONE SESSION OF EXERCISE

In contrast to the equivocal findings regarding the effects of endurance exercise training and a resultant increase in

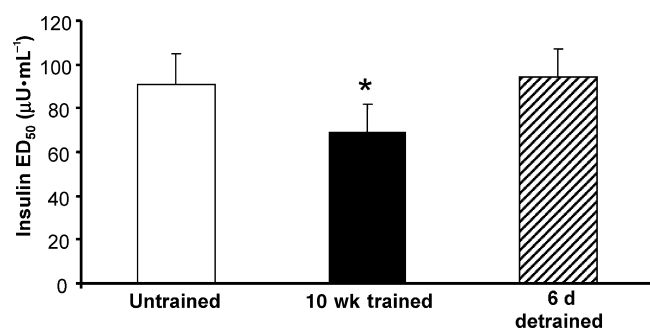


Figure 3. Figure demonstrating that the improvement in insulin sensitivity after endurance exercise training is short lived. Ten weeks of one-legged endurance exercise training increased insulin sensitivity in the trained leg (Insulin median effective dose = effective dose of insulin required to reach half-maximal rates of glucose disposal). After only 6 days without exercise, insulin sensitivity returned to untrained levels. *Significantly different from untrained and 6d detrained $P < 0.05$. (Adapted from Dela, F., K.J. Mikines, M. von Linstow, N.H. Secher, and H. Galbo. Effect of training on insulin-mediated glucose uptake in human muscle. *Am J Physiol Endocrinol Metab* 263:E1134–1143, 1992. Copyright © 1992 The American Physiological Society. Used with permission.)

fatty acid oxidative capacity on insulin sensitivity, it is well established that a single session of exercise can improve insulin sensitivity for several hours and even days (3), as long as the exercise session does not induce muscle damage/injury (12). Much of this insulin-sensitizing effect of a single session of exercise has been associated with a reduction in muscle glycogen concentration. When muscle glycogen concentration is increased above preexercise levels in lean animals the day after exercise, the improvement in insulin sensitivity is reversed (3). This suggests that the exercise-induced improvement in insulin sensitivity that is often found the day after exercise in lean animals may rely largely on muscle glycogen status. However, as discussed above, insulin sensitivity in obese individuals is suppressed in large part because of their excessive fatty acid availability. Therefore, in obesity, in addition to an exercise-induced reduction in muscle glycogen concentration, there is potential for a single session of exercise to relieve some of the fatty acid-induced insulin resistance. Indeed, acute exercise has been found to markedly increase insulin sensitivity in obese individuals, despite elevated fatty acid availability (5). Similarly, we have recently reported that a single session of exercise protects against fatty acid-induced insulin resistance in nonobese subjects infused with lipid and heparin to increase plasma fatty acid concentrations to levels similar to that found in abdominal obesity (20).

How acute exercise protects against fatty acid-induced insulin resistance is still not completely understood. In our recent study (20), we found that the exercise-induced improvement in insulin sensitivity was accompanied by a greater than 50% increased intramyocellular triglyceride (IMTG) concentration, with a concomitant reduction in the accumulation of intramyocellular fatty acid intermediates (*i.e.*, ceramide and diacylglyceride), and a reduction in markers for the activation of proinflammatory pathways (*i.e.*, *p*-JNK, I κ B/NF- κ B) (20). These findings led us to the novel hypothesis that the partitioning of fatty acids toward storage in IMTG may actually help protect against an inflammatory response and insulin resistance by reducing substrate for the formation of intracellular fatty acid intermediates (20). It is important to note that the increased insulin-mediated glucose uptake in obese individuals after exercise can occur independently of enhanced insulin signaling. Therefore, the exercise-induced improvements in insulin action can also be attributed to alternative mechanisms (*e.g.*, increased abundance and redistribution of glucose transporter protein abundance (GLUT 4) and other intracellular signaling pathways).

Our hypothesis that formation of IMTG synthesis may actually improve glucose uptake is contrary to many commonly held notions about the effect of IMTG on insulin sensitivity. Several studies have demonstrated strong correlations between IMTG concentration and insulin resistance in obese subjects (*e.g.*, (8)). Although, initially, several studies suggested a cause-and-effect relationship between IMTG concentration and insulin resistance, many now suggest that the relationship is probably not causal, but rather IMTG may have an indirect effect on impairing insulin sensitivity. One important discrepancy to the idea that IMTG may be involved (directly or indirectly) with the

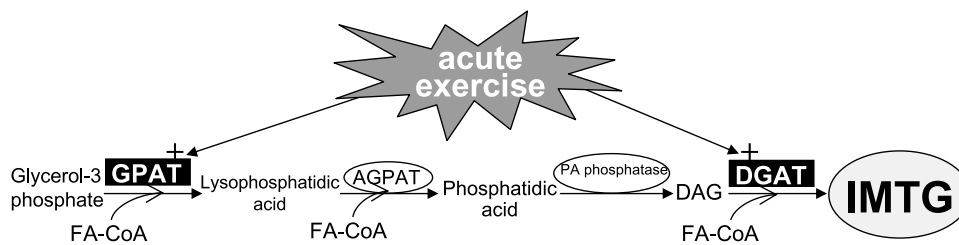


Figure 4. Schematic diagram depicting the effect of a single session of exercise on the regulation of intramyocellular triglyceride (IMTG) synthesis. Acute exercise increased the protein abundance of mitochondrial glycerol-3-phosphate acyltransferase (mGPAT) and diacylglycerol acyltransferase (DGAT) (20), as well as the activity of DGAT (13) in skeletal muscle. AGPAT indicates 1-acylglycerol-3-phosphate acyltransferase; DAG, diacylglyceride; FA-CoA, fatty acyl-CoA; PA, phosphatidic acid.

development of insulin resistance is that endurance-trained athletes have both high IMTG concentrations and enhanced insulin sensitivity (commonly referred to as the “athlete’s paradox”) (8). However, rather than describing a paradox, we contend that the IMTG accumulation may not induce insulin resistance at all (either directly or indirectly), but rather the high IMTG concentration and the suppressed insulin sensitivity found in obese individuals are both the consequence of the same metabolic process, namely, excessive fatty acid availability and uptake into skeletal muscle. Alternatively, in trained athletes, an increased IMTG accumulation may represent an important adaptation to replenish energy stores in muscle after exercise, which does not seem to negatively affect insulin sensitivity. In fact, our novel hypothesis suggests that increased IMTG synthesis may actually be beneficial for enhancing insulin sensitivity by reducing the availability of intracellular substrate (*i.e.*, activated fatty acids) for formation of more harmful intracellular fatty acid intermediates. This hypothesis is somewhat analogous to the finding that insulin resistance in lipodystrophic animals (*i.e.*, animals that cannot store fatty acid in adipose tissue) was eliminated after surgical implantation of adipose tissue into these animals (7). Implanting adipose tissue allowed the animals to store fatty acids in triglycerides within adipocytes, thereby reducing the availability of fatty acids for alternative metabolic fates in muscle and liver. It is reasonable to surmise that when fatty acid availability is high, partitioning fatty acids that are entering the muscle cell toward storage in IMTG may be a relatively “safe” metabolic fate. Indeed, data from Bachmann *et al.* (2) demonstrated that when fat availability was increased through either diet or a lipid + heparin infusion, subjects with the greatest capacity to partition fatty acids toward IMTG storage had the smallest impairment in insulin sensitivity. A single session of exercise has been found to increase IMTG synthesis and storage when lipid availability is high. Our recent study is the first, to our knowledge, to demonstrate that a single exercise bout in human subjects (*i.e.*, 90 min of exercise at 65% peak oxygen uptake ($\dot{V}O_{2\text{peak}}$)) increased mitochondrial glycerol-3-phosphate acyltransferase (mGPAT) and diacylglycerol acyltransferase (DGAT) in skeletal muscle, which are key enzymes in the regulation of triglyceride synthesis (20). Therefore, this may help explain how a single session of exercise may repartition fatty acids that have entered the muscle cell toward storage as IMTG (Fig. 4)

rather than toward more metabolically “unfavorable” routes. In agreement with our findings, Liu *et al.* (13) reported that changes in DGAT expression and activity play a key role in the protection against fatty acid-induced insulin resistance. Importantly, this mechanism of repartitioning fatty acids toward storage as IMTG may only be relevant under conditions when fatty acid availability is high; thus, this may represent an important mechanism for the exercise-induced improvements in insulin sensitivity that can persist into the next day in obese individuals.

Our recent findings corroborate a recent study that found that a single session of exercise reversed insulin resistance in rats fed with a high-fat diet, with a parallel reduction in proinflammatory/stress (16). Therefore, these data further support the notion that acute exercise can attenuate the lipid-induced proinflammatory response in skeletal muscle. Our findings, and those of Ropelle *et al.* (16), also suggest that much of the effects of exercise on reducing proinflammatory stress in skeletal muscle is due to the most recent session of exercise, rather than an effect of chronic exercise training, and a subsequent improvement in oxidative capacity.

SUMMARY AND CONCLUSIONS

Excessive fatty acid availability, as found in obese individuals, can lead to insulin resistance, and the “partitioning” of these fatty acids within the muscle cell toward the accumulation of intracellular fatty acid intermediates can mediate this response. Although there is compelling evidence to suggest that impaired mitochondrial function and a resultant low oxidative capacity are associated with insulin resistance, whether increasing oxidative capacity via endurance exercise training improves insulin sensitivity remains controversial. Alternatively, the insulin-sensitizing effects of a single session of exercise are robust, suggesting that a substantial portion and perhaps most of the benefits of exercise on insulin sensitivity are not due to the adaptations accrued over weeks, months, or even years of endurance exercise training but stem largely from the most recent exercise session(s). Additionally, although IMTG concentration has been linked (directly and indirectly) with insulin resistance, this finding is far from universal. We propose an alternative hypothesis, suggesting that increasing the rate of IMTG synthesis after exercise

may actually help protect against insulin resistance by serving as a more favorable metabolic fate for fatty acids entering the muscle cell, compared with formation and accumulation of fatty acid intermediates. It should be clarified that this hypothesis does not suggest that a large IMTG concentration directly helps improve insulin sensitivity, but rather that an increase in the active incorporation of fatty acids entering the myocyte into IMTG (such as that which occurs after a single exercise session) may be beneficial. Surprisingly, although it is well recognized that a single session of exercise can potentially enhance insulin sensitivity, the “dose” of exercise (e.g., exercise intensity and energy expended) necessary to evoke this response has not been well defined. A better understanding of the amount of exercise required to increase insulin sensitivity and the mechanisms underlying the regulation of insulin action after exercise would provide very valuable information for the development of lifestyle programs aimed to maximize the important metabolic benefits of each exercise session in obese and insulin-resistant patients.

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CORRIGENDUM

Figure caption, Narici and Maganaris. Article printed in ESSR 35:3, July 2007.

An error was detected in the figure caption of “Plasticity of the Muscle-Tendon Complex With Disuse and Aging,” published in the July 2007 ESSR [35(3):126–134]. The correction is listed below:

- Page 128, Figure 3 caption should be listed [Adapted from Fluck, M., et al. Fibre-type specific concentration of focal adhesion kinase at the sarcolemma: influence of fibre innervation and regeneration. *J. Exp. Biol.* 205:2337–2348, 2002. Copyright © 2002 The Journal of Experimental Biology. Used with permission.], not as reprinted from (20).