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Exercise and obesity-induced insulin resistance in skeletal muscle

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ABSTRACT

The skeletal muscle in our body is a major site for bioenergetics and metabolism during exercise. Carbohydrates and fats are the primary nutrients that provide the necessary energy required to maintain cellular activities during exercise. The metabolic responses to exercise in glucose and lipid regulation depend on the intensity and duration of exercise. Because of the increasing prevalence of obesity, recent studies have focused on the cellular and molecular mechanisms of obesity-induced insulin resistance in skeletal muscle. Accumulation of intramyocellular lipid may lead to insulin resistance in skeletal muscle. In addition, lipid intermediates (e.g., fatty acyl-coenzyme A, diacylglycerol, and ceramide) impair insulin signaling in skeletal muscle. Recently, emerging evidence linking obesity-induced insulin resistance to excessive lipid oxidation, mitochondrial overload, and mitochondrial oxidative stress have been provided with mitochondrial function. This review will provide a brief comprehensive summary on exercise and skeletal muscle metabolism, and discuss the potential mechanisms of obesity-induced insulin resistance in skeletal muscle.

1. Introduction

The prevalence of obesity has reached epidemic proportions worldwide, and is threatening to become a global epidemic, suggesting that obesity is spreading to all regions of the world and is imposing an enormous economic (cost) burden on many countries for its treatment and/or prevention. In the modern society, obesity induced by high-caloric/high-fat diet (HFD) and reduced physical activity results in a serious health threat because of the increased risk of developing chronic diseases such as cardiovascular disease, diabetes, and cancer, all of which are associated with insulin resistance. Skeletal muscle plays an important role in regulating whole-body homeostasis. For example, skeletal muscle is responsible for approximately 80% of the postprandial clearance of glucose.[1]

In the development of obesity and type II diabetes: (1) insulin secretion from beta cell is impaired; (2) hepatic glucose production from liver is increased; and (3) peripheral glucose utilization in muscle is decreased.[2] In particular, obesity-induced insulin resistance in skeletal muscle is a multifactorial process. So far, it is unclear which specific mechanism(s) is responsible for obesity-induced insulin resistance. However, a number of contributing factors have been suggested. In this paper, we will summarize some potential mechanisms of obesity-induced insulin resistance in skeletal muscle.

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Exercise training has been well known to provide benefits as a potential intervention for obesity-related chronic diseases, impaired contractile function, and risk of muscle injury. In addition, regular exercise training has many desirable effects for people with obesity and type II diabetes, suggesting that physical activity decreases insulin resistance and increases insulin sensitivity in skeletal muscle.[3–5] Although previous data showed the beneficial effects of exercise on insulin sensitivity in obese skeletal muscle, the exact mechanism(s) by which exercise protects against obesity-induced insulin resistance in skeletal muscle has not yet been fully understood. Therefore, in the next section, an overview of the role of exercise in obesity-induced insulin resistance in skeletal muscle will be provided.

2. Characteristics of skeletal muscle fibers and exercise

Skeletal muscle contains two different kinds of fibers, which provide different speeds of contraction and ability of producing force,[6] namely, type I (slow fiber or slow-twitch fiber) and type II [fast fiber or fast-twitch (FT) fiber]. Furthermore, the type II fibers consist of two isoforms. In humans, type II fibers are classified into FT type a (type IIa) and FT type x (type IIx). However, in animals, type IIb is used instead type IIx. The type I and type II fibers have different speeds of contraction due to different forms of myosin adenosinetriphosphatase (ATPase). Myosin ATPase is the enzyme that splits ATP to produce energy for muscle contraction. For example, type I fibers have a slow form of myosin ATPase, whereas type II fibers have a fast form of myosin ATPase.[6] Therefore, ATP is split more rapidly in type II fibers than in type I fibers in response to neural stimulation for muscle contraction.

In general, most muscles in our body consist of approximately 50% type I fibers and 50% type II fibers.[7] However, the exact percentage of each fiber type varies in various muscles. In addition, the percentage of each fiber type varies from one individual to another. For example, power athletes (e.g., track sprinters) typically possess a large percentage of fast fibers, whereas endurance athletes generally have a high percentage of slow fibers.[8,9] Although muscle fiber types are known to play a role in sport performance, an individual's muscle fiber composition is not the only factor that determines success in athletic events. In fact, successful athletes have considerable interaction of physiological, psychological, neurological, cardiopulmonary, and biomechanical factors.

In general, type I fibers have a high level of aerobic endurance as well as very high efficiency at generating ATP from the oxidation of carbohydrate and fat for muscle fiber contraction and relaxation.[10] Type I fibers can continuously produce ATP during periods of oxidation. Because type I fibers have high aerobic endurance, they are recruited very often during low-intensity endurance events (e.g., marathon) and during most daily activities (e.g., walking). By contrast, type II fibers have relatively low aerobic endurance compared with type I fibers.[10] Type II fibers are recruited to perform in the absence of adequate oxygen (i.e., in anaerobic conditions), and they play a major role in high-intensity exercise. For example, type II fibers are the primary fiber type for short, high-intensity power athletes (e.g., sprinters).

3. Exercise and bioenergetics in skeletal muscle

Our body uses carbohydrate, fat, and protein substrates to provide the necessary energy to maintain cellular activities both at rest and during exercise. The primary nutrients during exercise are carbohydrates and fats, with protein contributing a relatively small amount of the total used energy.[11] Exercise provides a big challenge to the bioenergetics in the working muscle. The body's total energy expenditure during exercise may increase by 15–25 times above expenditure at rest. Most of the energy production is used to produce ATP for the contraction of skeletal muscle. Similar to this process, skeletal muscle can generate and consume large quantities of ATP during exercise.

The metabolic responses to exercise are affected by the intensity and duration of exercise.[6] For example, during high-intensity, short-term exercise (i.e., 2–20 seconds), most of the ATP in muscle is generated by the ATP–phosphocreatine system. During periods of intense exercise (i.e., > 20 seconds), much of the needed ATP is produced by anaerobic glycolysis. However, during periods of prolonged exercise (i.e., > 10 minutes), the energy comes primarily from aerobic metabolism.

Carbohydrate as glycogen is stored in the skeletal muscle and liver. The direct source of carbohydrate for muscle energy metabolism is provided by muscle glycogen, whereas liver glycogen is served to replace blood glucose.[12] For example, when blood glucose levels decrease during periods of prolonged exercise, glucose by liver glycogenolysis is released into the blood to maintain blood glucose levels, which is transported to the working skeletal muscle as fuel. The relative contribution of blood glucose and muscle glycogen during exercise for energy metabolism depends on the intensity and duration of exercise.[10] During low-intensity exercise, blood glucose works predominantly, whereas during high-intensity exercise, muscle glycogen plays the greater role for energy metabolism. In addition, muscle glycogen is the primary source of carbohydrate during the 1st hour of submaximal prolonged exercise. However, blood glucose works predominantly as a fuel due to the decline in muscle glycogen levels.

Most fat as triglycerides is stored in adipocytes (fat cells). However, some fat is also stored in skeletal muscle.[7] For energy metabolism during exercise, triglycerides are divided into free fatty acid (FFA) and glycerol. The FFA is converted into acetyl-coenzyme A (CoA) in the Krebs cycle to produce ATP. Like carbohydrate, the intensity and duration of exercise determine the relative contribution of adipocytes (plasma FFA) and muscle (triglycerides) for energy metabolism.[10] For example, during low-intensity exercise, the primary source of fat is plasma FFA (i.e., FFA from adipocytes), whereas during high-intensity exercise, muscle triglycerides play the greater role for energy metabolism. In addition, the contribution of plasma FFA and muscle triglycerides is very similar at the beginning of exercise. However, as the duration of exercise increases, plasma FFA plays the greater role as a fuel source.

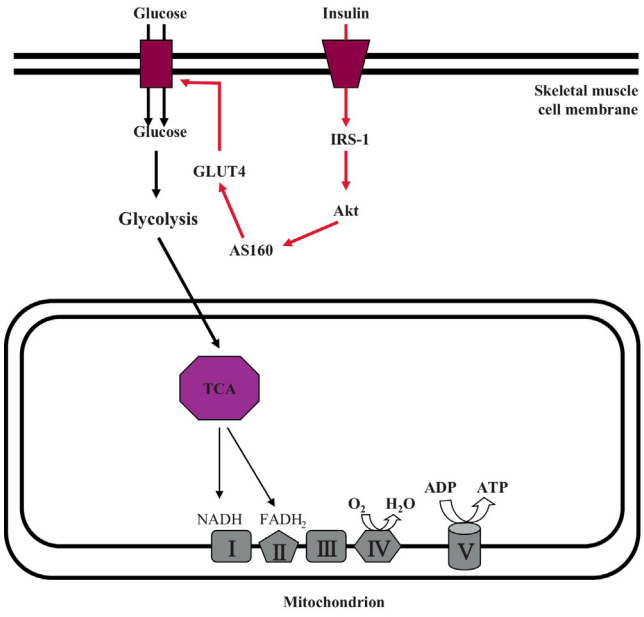

Fig. 1 – Insulin signaling in skeletal muscle. ADP, adenosine diphosphate; Akt, protein kinase B; AS160, Akt substrate of 160 kDa; ATP, adenosine triphosphate; $FADH_2$, flavin adenine dinucleotide reduced; GLUT4, glucose transporter protein 4; IRS-1, insulin-receptor substrate-1; NADH, nicotinamide adenine dinucleotide reduced; TCA, tricarboxylic acid.

4. Glucose and lipid metabolism in skeletal muscle

Skeletal muscle is the major site that uses both glucose and lipid as fuel sources for energy metabolism. After a meal, approximately two-thirds of ingested glucose is taken up by skeletal muscle through an insulin-dependent mechanism.[13] In general, the plasma insulin concentration determines the contribution of glucose and lipid as fuel sources. For example, following glucose ingestion with meal, the elevation in plasma glucose concentration stimulates insulin secretion from the beta cell and insulin stimulates glucose uptake through insulin signaling in skeletal muscle.[14]

In normal skeletal muscle metabolism, insulin stimulates Akt phosphorylation through insulin-receptor substrate-1 (IRS-1) and phosphatidylinositol 3-kinase (PI3K), and activated Akt phosphorylates Akt substrate 160 (AS160) allowing glucose transporter protein 4 (GLUT4) storage vesicles to move to the plasma membrane for glucose.[15–18] There are five major isoforms of GLUTs. Only GLUT4 is found in the skeletal muscle. After the uptake of glucose into the skeletal muscle through the GLUT4 vesicles, glucose is immediately phosphorylated by hexokinase, and the phosphorylated glucose is stored as glycogen or enters into the glycolytic pathway for oxidation in mitochondria through the tricarboxylic acid cycle and electron transport system (Fig. 1). However, during conditions of fasting, at which muscle glucose uptake is reduced and the plasma FFA is elevated, FFA serves as the major fuel source for energy metabolism in skeletal muscle. Once the FFA enters the skeletal muscle through fatty acid translocase/CD36 and fatty acid–binding protein, they are activated by long-chain acyl-CoA synthetase to form a fatty acyl-CoA (FA-CoA), which is then partitioned toward the synthesis of lipid [triacylglycerol (TAG)] in the cytoplasm or toward mitochondria for oxidation in the presence of carnitine palmitoyltransferase 1 and carnitine palmitoyltransferase 2 (Fig. 2).[19] Thus, the ability of skeletal muscle to switch from glucose oxidation during a mixed meal state to fat oxidation during the fasting state is referred to as metabolic flexibility.[20]

5. Obesity and insulin resistance

Obesity is associated with a number of alterations in skeletal muscle metabolism leading to insulin resistance. However, it remains unclear which specific mechanism(s) is responsible for obesity-induced insulin resistance. The following discussion will highlight some potential mechanisms of obesity-induced insulin resistance in skeletal muscle in terms of mitochondrial role in the cells: (1) mitochondrial-independent mechanisms; and (2) mitochondrial-dependent mechanisms.

5.1. *Mitochondrial-independent mechanisms*

Although the exact mechanism that leads to the development of insulin resistance in skeletal muscle is not yet fully understood, increased intracellular fat content and lipid metabolites have been shown to play a primary role in skeletal muscle insulin resistance, independent of mitochondria.[21–23]

5.2. *Accumulation of intramyocellular lipid*

It has been reported that TAG in skeletal muscle is a prominent marker in the development of insulin resistance showing a negative relationship between intramyocellular lipid (IMCL) concentration and insulin sensitivity in nonobese adults.[24] An imbalance between fatty acid oxidation (FAO) and fatty acid synthesis could lead to lipid accumulation within the skeletal muscle, leading to insulin resistance. However, other data suggest that this is not a simple cause-and-effect mechanism. For example, endurance athletes show both high insulin sensitivity and elevated IMCL levels.[25] In addition, the overexpression of diacylglycerol acyltransferase producing TAG from diacylglycerol (DAG) and FA-CoA in the skeletal muscle of mice has been reported to increase both TAG and insulin sensitivity.[26] Therefore, IMCL does not appear to be a marker of insulin resistance in skeletal muscle.

5.3. *Accumulation of lipid intermediates (e.g., FA-CoA, DAG, and ceramide)*

The insulin signaling is responsible for insulin-mediated glucose transport into the cells. Indeed, much attention has been recently focused on lipid intermediates such as acyl-CoA, DAG, or ceramides that inhibit insulin signaling, which are attractive mediators of insulin resistance in

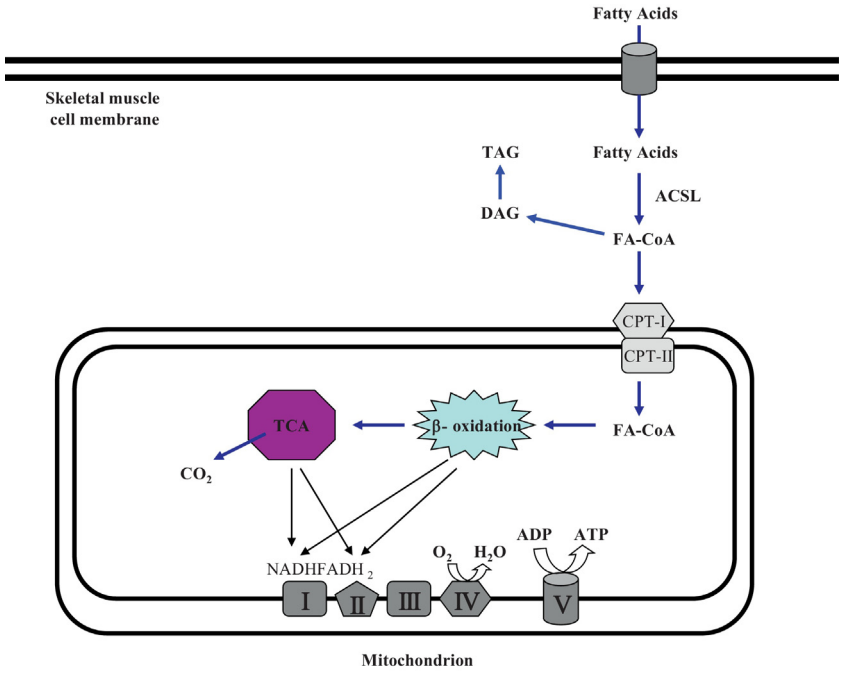

Fig. 2 – Fatty acid synthesis and oxidation signaling in skeletal muscle. ACSL, long-chain acyl-CoA synthetase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CPT-I, carnitine palmitoyltransferase 1; CPT-II, carnitine palmitoyltransferase 2; DAG, diacylglycerol; FA-CoA, fatty acyl-CoA; $FADH_2$, flavin adenine dinucleotide reduced; NADH, nicotinamide adenine dinucleotide reduced; TAG, triacylglycerol; TCA, tricarboxylic acid.

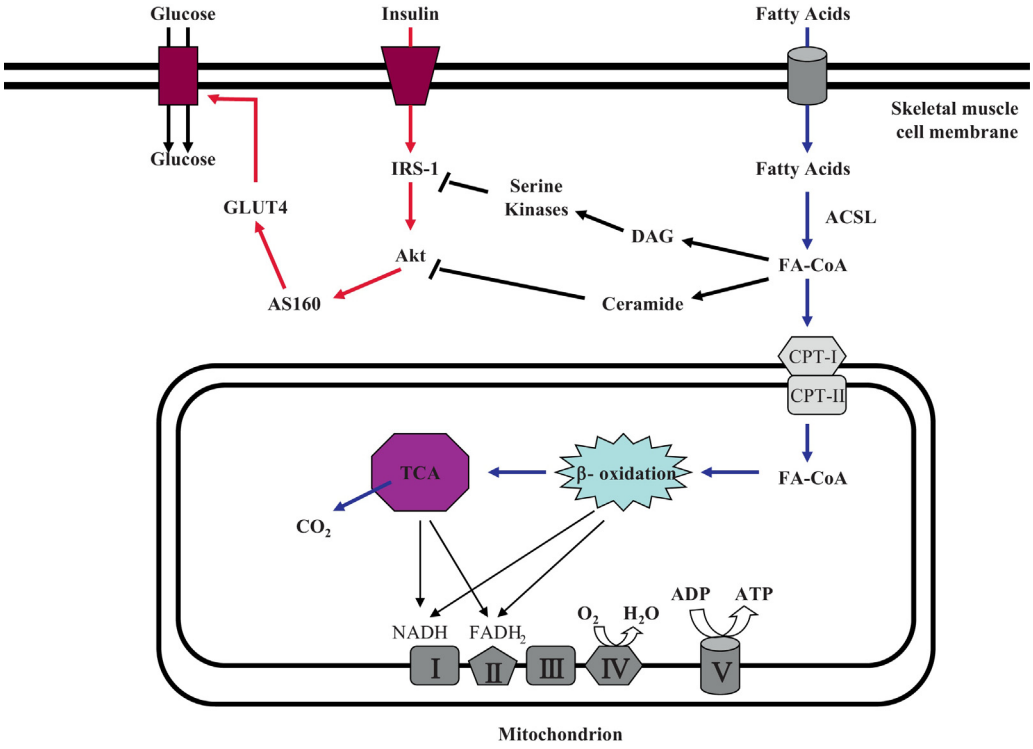

Fig. 3 – Effects of lipid intermediates (e.g., FA-CoA, DAG, ceramide) on insulin signaling in skeletal muscle. FA-CoA or DAG activates serine/threonine kinases, which phosphorylate serine IRS-1 leading to the impairment of insulin signaling. In addition, ceramide inhibits Akt phosphorylation leading to reduced glucose uptake. ACSL, long-chain acyl-CoA synthetase; ADP, adenosine diphosphate; Akt, protein kinase B; AS160, Akt substrate of 160 kDa; ATP, adenosine triphosphate; CPT-I, carnitine palmitoyltransferase 1; CPT-II, carnitine palmitoyltransferase 2; DAG, diacylglycerol; FA-CoA, fatty acyl-CoA; $FADH_2$, flavin adenine dinucleotide reduced; GLUT4, glucose transporter protein 4; IRS-1, insulin-receptor substrate-1; NADH, nicotinamide adenine dinucleotide reduced; TCA, tricarboxylic acid.

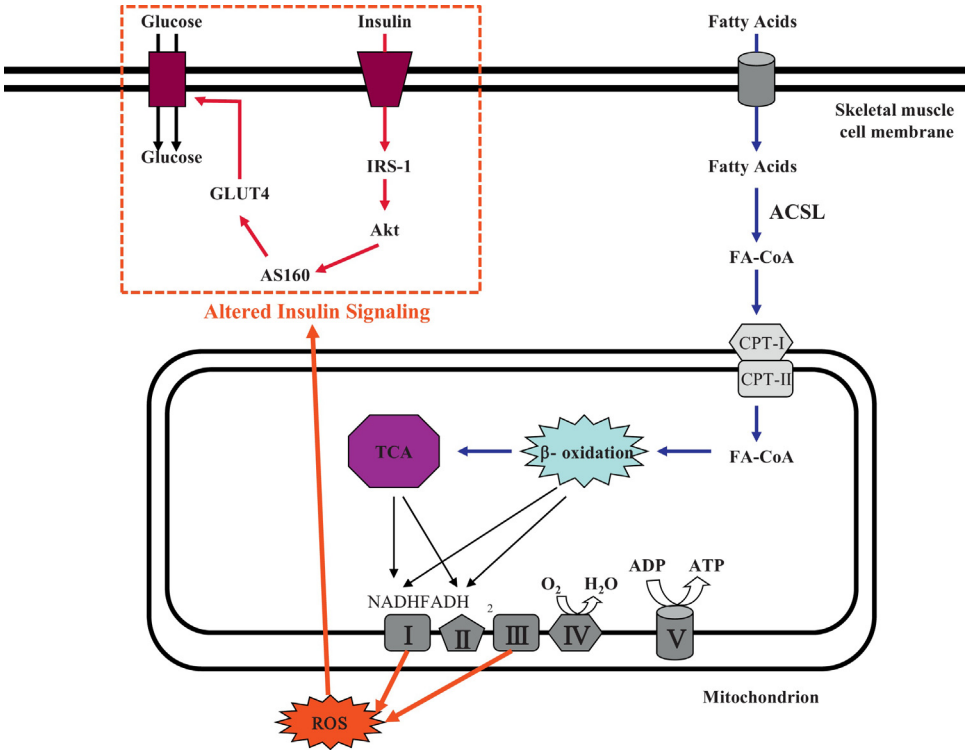

Fig. 4 – Effects of ROS on insulin signaling in skeletal muscle. ROS induced by electron transport system (complexes I and III) alters insulin signaling leading to insulin resistance. ACSL, long-chain acyl-CoA synthetase; ADP, adenosine diphosphate; Akt, protein kinase B; AS160, Akt substrate of 160 kDa; ATP, adenosine triphosphate; CPT-I, carnitine palmitoyltransferase 1; CPT-II, carnitine palmitoyltransferase 2; FA-CoA, fatty acyl-CoA; $FADH_2$, flavin adenine dinucleotide reduced; GLUT4, glucose transporter protein 4; IRS-1, insulin-receptor substrate-1; NADH, nicotinamide adenine dinucleotide reduced; ROS, reactive oxygen species; TCA, tricarboxylic acid.

skeletal muscle.[21–23] These emphasize that diminished fatty acid import and oxidation in mitochondria are a pivotal regulator in skeletal muscle insulin resistance, favoring activation of serine/threonine kinases (e.g., IκB kinase, c-Jun N-terminal kinase, protein kinase C theta) or ceramides that impair insulin signaling in skeletal muscle.[17,27] For example, FA-CoA or DAG activates serine/threonine kinases, which phosphorylate serine IRS-1 leading to insulin resistance.[16] In addition, FFA produces sphingolipids (ceramides), which inhibit Akt phosphorylation leading to reduced glucose uptake (Fig. 3).[28–31]

5.4. *Mitochondrial-dependent mechanisms*

Although many studies indicated that diminished mitochondrial function is associated with the development of insulin resistance in skeletal muscle,[32–34] others also have challenged the notion that a reduction of mitochondrial oxidative capacity plays an essential role between obesity and insulin resistance,[35–38] indicating that impairment of mitochondrial metabolism was not responsible for insulin resistance in skeletal muscle. However, the following two mechanisms are emerging evidence that obesity-induced insulin resistance in skeletal muscle is principally driven by mitochondrial overload and oxidative stress rather than oxidative capacity in mitochondria.

5.5. *Mitochondrial overload*

In normal mitochondria, FFAs enter mitochondria to produce acetyl-CoA during β-oxidation, which undergoes additional processes including Krebs cycle and electron transport chain (ETC) in the mitochondrial matrix, leading to CO_2 production in the Krebs cycle and ATP generation in the ETC. However, too much FFA intake (i.e., excessive β-oxidation) induces a lipid burden on mitochondria (called mitochondrial overload), and the mitochondria produces partially oxidized fatty acid such as acylcarnitine (called incomplete FAO).[39] This incomplete FAO may contribute to lipid-induced impairments in insulin action. For example, Koves et al[40] suggested that insulin resistance was associated with increased incomplete FAO in skeletal muscle. They showed the connection between the development of insulin resistance and lipid-induced mitochondrial overload by incomplete FAO in skeletal muscle. However, the precise connection between increased β-oxidative by-products and insulin resistance is not clear so far.

5.6. *Mitochondrial oxidative stress*

Metabolic oversupply (e.g., HFD and obesity) and reduced energy demand (e.g., physical inactivity) are major risk factors for insulin resistance and type 2 diabetes. Emerging evidence

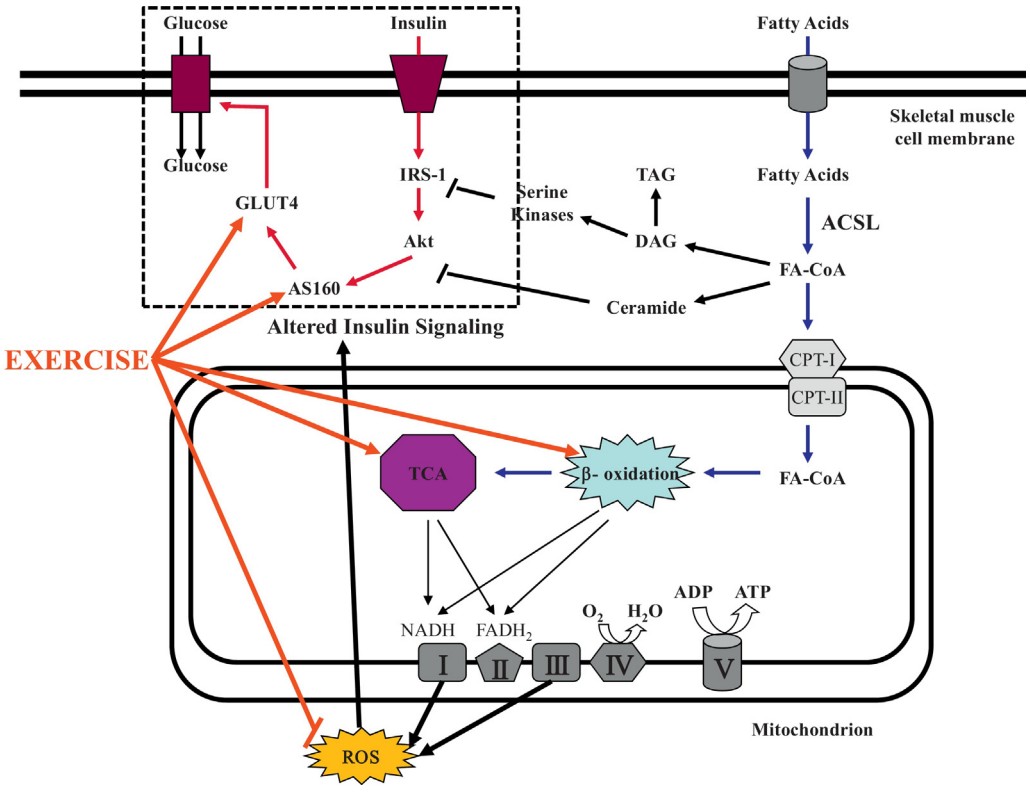

Fig. 5 – Effects of exercise on mitochondrial function and insulin signaling in skeletal muscle. Exercise increases fatty acid oxidation (e.g., β-oxidation and TCA) and protects against obesity-induced ROS, which impairs insulin signaling in skeletal muscle. In addition, exercise activates AS160 and GLUT4 resulting in increased insulin sensitivity. ACSL, long-chain acyl-CoA synthetase; ADP, adenosine diphosphate; Akt, protein kinase B; AS160, Akt substrate of 160 kDa; ATP, adenosine triphosphate; CPT-I, carnitine palmitoyltransferase 1; CPT-II, carnitine palmitoyltransferase 2; DAG, diacylglycerol; FA-CoA, fatty acyl-CoA; $FADH_2$, flavin adenine dinucleotide reduced; GLUT4, glucose transporter protein 4; IRS-1, insulin-receptor substrate-1; NADH, nicotinamide adenine dinucleotide reduced; ROS, reactive oxygen species; TAG, triacylglycerol; TCA, tricarboxylic acid.

indicates that overnutrition results in elevated mitochondrial oxidative stress (i.e., reactive oxygen species or ROS), which is the primary factor for the development of insulin resistance in skeletal muscle (Fig. 4).[41,42] Too much energy supply induces excessive production of nicotinamide adenine dinucleotide reduced (NADH) and flavin adenine dinucleotide reduced ($FADH_2$) through β-oxidation in mitochondria. These increased NADH and $FADH_2$ levels may be surplus-reducing equivalents. In other words, if β-oxidation is increased by oversupply of fatty acids without a corresponding increase in energy demand, surplus-reducing equivalents are generated. These surplus-reducing equivalents are associated with increased mitochondrial membrane potential, leading to increased production of superoxide and hydrogen peroxide. This increased ROS may result in insulin resistance.[39,43] To confirm the implication of mitochondrial oxidative stress in skeletal muscle insulin resistance, we recently demonstrated that administration of a mitochondrial-targeted antioxidant [e.g., mitochondrial-targeted oxidant scavenger (SS31) and mitochondrial-targeted catalase] prevented HFD-induced insulin resistance in animal model,[41] suggesting that mitochondrial ROS is a critical factor in the etiology of HFD-induced insulin resistance in skeletal muscle. However, the cellular and molecular mechanisms of how oxidative stress causes insulin resistance are still largely unknown. Redox-sensitive protein modifications may be a crucial mechanism for determining how oxidative stress regulates the insulin-signaling cascade with obesity.[43] In the near future, linking mitochondrial bioenergetics with insulin resistance will provide a mechanistic basis for the clinical strategies in treating obesity-induced insulin resistance.

6. Exercise and insulin resistance

The development of insulin resistance in skeletal muscle is associated with impairments at a number of key regulatory steps with obesity in the abovementioned factors, including elevated IMCL, lipid intermediates (e.g., FA-CoA, DAG, ceramide), mitochondrial overload, and mitochondrial ROS. However, exercise is widely recognized as having beneficial effects on cardiovascular, respiratory, metabolic, and neuromuscular health. Furthermore, emerging evidence suggests that exercise protects against obesity-induced insulin resistance (Fig. 5).

Obesity is associated with lower rates of skeletal muscle FAO, which is linked to insulin resistance. However, exercise training increases FAO in skeletal muscle of obese individuals.[4,44,45] For example, Bajpeyi et al[46] indicated that IMCL was elevated in obese and diabetic individuals. However, after 10 days of exercise training, IMCL content was significantly decreased. Houmard et al[47] also found that 10 days of short-term exercise training stimulated PI3K activity that resulted in improved insulin sensitivity in sedentary obese individuals. In addition, 12 weeks of exercise training increased insulin action and reversed impairment of AS160 phosphorylation in insulin-resistant aged individuals.[5] In the same way, GLUT4 gene expression was higher in the skeletal muscle of endurance-trained individuals than sedentary individuals.[48]

Furthermore, improvements in mitochondrial function have been observed in sedentary obese individuals after exercise training.[49,50] Recently, we also found that a long-term HFD caused an increased skeletal muscle H_2O_2 emission, in conjunction with the development of insulin resistance in rodents. However, mild exercise training attenuated HFD-induced H_2O_2 elevation and insulin resistance in skeletal muscle,[51] suggesting that increased energy expenditure (e.g., exercise) is fundamental to the preservation of mitochondrial function/integrity and/or for preventing oxidative stress on a daily basis.

Interestingly, exercise mode has differential effects on body composition and insulin resistance. For example, Willis et al[52] demonstrated that aerobic training was the optimal mode of exercise for reducing fat mass and body mass, whereas resistance training was needed for increasing lean mass in obese individuals. Furthermore, Slentz et al[53] showed that aerobic exercise was more effective than resistance exercise at improving visceral fat, total abdominal fat, and insulin resistance. However, Slentz et al[54] observed that both moderate and vigorous exercise training improved pancreatic beta-cell function in sedentary and overweight individuals.

7. Conclusions

Skeletal muscle is the primary tissue to use both glucose and lipid as fuel sources to regulate insulin sensitivity in our body. Obesity plays a pivotal role in the pathogenesis of insulin resistance in skeletal muscle. Obesity-induced insulin resistance in skeletal muscle results from various potential mechanisms including accumulation of IMCL and lipid intermediates (e.g., FA-CoA, DAG, and ceramide), mitochondrial overload-induced incomplete FAO, and mitochondrial oxidative stress. Exercise represents one of the most effective means of reversing insulin resistance in skeletal muscle of obese patients at high risk for type II diabetes. However, further research is necessary to determine the cellular and molecular mechanisms by which exercise training protects against obesity-induced insulin resistance in skeletal muscle.

Conflicts of interest

There are no conflicts of interest to declare.

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