

REVIEW ARTICLE

Molecular mechanisms by which aerobic exercise induces insulin sensitivity

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Abstract

Insulin resistance is a key feature of Type 2 diabetes and an important therapeutic target to address glycemic control to prevent diabetic complications. Lifestyle advice is the first step in the ADA/EASD consensus guidelines followed by metformin therapy. Aerobic exercise (AE) can increase insulin sensitivity by several molecular pathways including upregulation of insulin transporters in the cellular membrane of insulin-dependent cells. In addition, AE improves insulin sensitivity by amelioration of the pathophysiologic pathways involved in insulin resistance such as the reduction of adipokines, inflammatory and oxidative stress responses, and improvement of insulin signal transduction via different molecular pathways. This review details the molecular pathways by which AE induces beneficial effects on insulin resistance

KEYWORDS

adipokines, aerobic exercise, inflammation, insulin resistance, insulin signal transduction, oxidative stress

1 | INTRODUCTION

The global prevalence of Type 2 diabetes (T2D) is increasing rapidly (Mayer-Davis et al., 2017) resulting in increased morbidity by diabetic complications (Yaribeygi, Katsiki, Behnam, Iranpanah, & Sahebkar, 2018) and high mortality. The development of T2D and its complications is having an increasing impact on the healthcare budget worldwide (Rosella et al., 2016). Improved glycemic control is central to prevent diabetic complications through different classes of therapeutic agents including exogenous insulin (Diabetes Prevention Program Research Group, 2015; Perreault et al., 2017; Yaribeygi, Katsiki, Butler, & Sahebkar, 2018d), though these may exhibit side effects (Ghadge et al., 2014; Seino et al., 2015). Lifestyle advice is the first line of therapy in the

ADA/EASD consensus guidelines that includes aerobic exercise (AE) (American Diabetes Association, 2015).

AE has been suggested to be an important component in diabetes care for the prevention of microvascular/macrovacular outcomes (Karstoft & Pedersen, 2016) through improved glycemic control by the increase in peripheral insulin sensitivity (Karstoft & Pedersen, 2016; Sylow, Kleinert, Richter, & Jensen, 2017; Yang et al., 2014). AE exerts these beneficial effects through several molecular mechanisms (Chaturvedi, Kalani, Medina, Familtsava, & Tyagi, 2015; Chetan et al., 2018; Sylow et al., 2017). AE is a low-intensity and high-duration physical activities that is dependent on oxygen consumption providing energy as adenosine triphosphate (ATP; Yang et al., 2014). This type of training is completely dependent on the availability of oxygen (Yang et al., 2014). Such

TABLE 1 The roles of aerobic exercise in glucose homeostasis

Molecular mechanisms	Possible role of aerobic exercise
Adipokines	Consumption of free fatty acids as metabolic substrate reduces adipokine generation, reducing inflammation, and improving insulin resistance
Oxidative stress	Improvement of the redox state and reducing oxidative stress-induced insulin resistance
Glut-4 localization	Upregulation of GLUT-4 in cell membrane of insulin-dependent cells
Ceramide level	Reduction of plasma levels of ceramide and prevention of ceramide-induced insulin resistance
IRS-1 phosphorylation	Increased IRS-1 phosphorylation leading to improvement of insulin signal transduction
Improvement of β cell function/mass	Improves islets function, maintains β cell mass and prevention of apoptosis in islets
Capillarization	Induction of angiogenesis in skeletal muscle leading to higher glucose uptake by myocytes

Note. GLUT-4: glucose transporter protein; IRS-1: insulin receptor substrate 1.

physical activities include cycling, swimming, walking, jogging, running, and mountaineering (Siasos et al., 2016), in contrast to high-intensity short-term physical training such as bodybuilding exercises that are of short duration anaerobic exercise (Ahtiainen et al., 2018; Yardley et al., 2013), in which glucose is the main metabolic substrate, while in AE, fatty acids are the main substrate consumed (Hall, 2015).

2 | INSULIN SIGNAL TRANSDUCTION (IST)

IST is initiated by the binding of insulin to the α chain of the insulin receptor (IR). The IR is a member of the transmembrane tyrosine kinase and is composed of two chains, α and β , that is bound to by insulin and less so by insulin-like growth factor 1 and 2 (IGF 1 and 2; Færch et al., 2016). Binding of insulin to the IR induces structural changes in the β chain leading to autophosphorylation in tyrosine residues followed by downstream recruitment of different adaptor proteins that is, insulin receptor substrates (IRSs), SHC-transforming protein, and adapter protein with a PH and SH2 domain protein (Hall, 2015; Kiselyov, Versteyhe, Gauguin, & De Meyts, 2009), forming the binding site for IRS-1 (Kiselyov et al., 2009). Various types of insulin-dependent kinases such as extracellular signal-regulated kinase 1/2, atypical protein kinase C, ribosomal protein S6 kinase β -1, serine/threonine-protein kinase 2, AKT, mammalian target of rapamycin, and rho-associated protein kinase, and other types of kinases such as 5' AMP-activated protein kinase (AMPK) and glycogen synthase kinase 3 may phosphorylate IRSs causing its activation (Copps & White, 2012; Kiselyov et al., 2009). Activated IRS-1 activates phosphoinositide 3-kinase that catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-trisphosphate (PIP₃; Ho, Sriram, & Dipple, 2016). PIP₃ is itself a potent activator for protein kinase B (also known as Akt) that facilitates glucose entry into the cell by translocation of glucose transporter protein 4 (GLUT-4) to the cell membrane and inhibits glycogen synthase kinase leading to glycogen synthesis (Ho et al., 2016; Koeppen & Stanton, 2017).

3 | AE AND GLUCOSE HOMEOSTASIS

A sedentary lifestyle and associated obesity have been related to the increase in the prevalence of T2D (American Diabetes Association, 2015), contributed to by long-term periods of immobility during daily work (Eaton & Eaton, 2017). Increasing evidence has shown that this sedentary lifestyle is related to the increased risk of insulin resistance leading to T2D (Eaton & Eaton, 2017). The promotion of AE is widely suggested by physicians to augment medical therapy to optimize glycemic control (Mitranun, Deerochanawong, Tanaka, & Suksom, 2014), AE improves insulin sensitivity in insulin-dependent peripheral tissues in adipocytes, cardiomyocytes, and myocytes (Ryan et al., 2014).

IST is a complex process mediating the entry of glucose into the cell and its impairment leads to insulin resistance (Gu, Liu, Zhang, & Zhang, 2014). Reports have identified key signaling molecules and pathways affected by AE (Bird & Hawley, 2017). AE may improve IST by either direct or indirect mechanisms (Table 1) and molecular pathways by which AE induces insulin sensitivity are detailed below.

3.1 | Adipokines and insulin resistance: Possible roles of AE

Inflammation and higher levels of circulatory inflammatory mediators have been implicated in the pathogenesis of T2D (Tomić, Vrabec, Ljubić, Blaslov, & Smirčić-Duvnjak, 2013; Yaribeygi et al., 2018d), with activation of the innate immune system (Donath, 2014; Tomić et al., 2013). In this context, inhibition of inflammation by antidiabetic drugs may synergize their hypoglycemic effects (Donath, 2014). Inflammation is a potential link between obesity and insulin resistance through the release of inflammatory mediators released by adipose tissue (i.e., adipokines) and other peripheral tissues (tumor necrosis factor- α [TNF- α], interleukin-6 [IL-6], and monocyte chemoattractant protein-1; Antuna-Puente, Fève, Fellahi, & Bastard, 2008; Yaribeygi, Farrokhi, Butler, & Sahebkar, 2018).

Adipokines are a family of cytokines (leptin, adiponectin, resistin, and visfatin) that are released mainly by activated macrophages of

adipocytes. They play an essential role in the development of insulin resistance and T2D, and are associated with an increased risk of obesity-related cardiovascular disease (Antuna-Puente et al., 2008; Fantuzzi, 2005). Additional cytokines associated with obesity include IL-8, IL-10, interferon γ (INF- γ), and inducible protein 10 (or C-X-C motif chemokine 10; Azar Sharabiani et al., 2011; Scherer, Williams, Fogliano, Baldini, & Lodish, 1995). Adipose tissue is the main storage of the inflammatory mediators, and adipokine levels increase as adipose tissue mass increases (Antuna-Puente et al., 2008; Trayhurn & Beattie, 2001). Therefore, reducing body mass index leads to suppression of inflammation-induced insulin resistance and results in enhanced insulin sensitivity (Azar Sharabiani et al., 2011; Yaribeygi, Farrokhi, et al., 2018). AE can effectively reduce total body fat by utilizing fatty acids as the main substrate, lowering circulating cytokine levels involved in insulin resistance (Hayashino et al., 2014; Lehri & Mokha, 2006).

A previous meta-analysis reported that AE decreased C-reactive protein (CRP) and IL-6 in T2D patients suggesting that AE might be a therapeutic option to improve inflammation-induced insulin resistance in diabetic patients (Hayashino et al., 2014). Kohut et al. (2006) demonstrated that AE significantly decreased circulating CRP, IL-6, IL-18, and TNF- α levels independent of β -adrenergic receptors and psychosocial factors (Kohut et al., 2006). Recently, Mattingly, Laitano, & Clanton (2018) demonstrated that chronic AE markedly reduced lipopolysaccharides-induced inflammation in mice. Moreover, Perandini et al. (2015) found that chronic AE significantly reduced the inflammatory cytokines INF- γ , IL-10, IL-6, and TNF- α in women. It should be noted that although AE may induce an inflammatory response acutely, repetitive AE causes significant suppression (Perandini et al., 2015; Silva et al., 2017). You et al. (2014) demonstrated that 20 weeks of AE reduced adipose tissue in the gluteal and abdominal areas and consequently decreased adiponectin production.

Long-duration AE programs with weight loss appear to be more effective in the reduction of adipokine secretion by adipocytes than acute periods of training that are accompanied with low or no weight loss (Silva et al., 2017; You et al., 2014). However, AE can decrease inflammatory mediators without any decline in total fat mass (Koh & Park, 2017). Koh & Park (2017) demonstrated that 4 weeks of AE markedly reduced the inflammatory cytokine TNF- α without any decrease in body weight. These data suggest that AE may modulate inflammatory mediators leading to lower inflammation-induced insulin resistance and increase insulin sensitivity in peripheral tissues.

3.2 | AE and GLUT-4 upregulation/function

GLUT-4 is an important glucose transporter dependent on insulin and is responsible for glucose entering into the adipocytes, myocytes, and cardiomyocytes; any failure in GLUT-4 expression and localization may result in impaired insulin signaling leading to insulin resistance (Ashrafi, Wu, Farrell, & Ryan, 2017; Gaster, Staehr, Beck-Nielsen, Schröder, & Handberg, 2001) and T2D development (Boden et al., 2015; Luna-Vital, Weiss, Gonzalez, & de Mejia, 2017). Conversely, any stimuli that enhance GLUT-4 expression will increase insulin sensitivity (Luna-Vital et al., 2017).

AE increases GLUT-4 expression in peripheral tissues (Richter & Hargreaves, 2013; Sylow et al., 2016; Yousefia, Bakhtiyarib, & Valizadeh, 2017) by upregulation in skeletal muscles via AMPK and Ca^{2+} /calmodulin-dependent protein kinase II (CaMK-II) signaling pathways (Richter & Hargreaves, 2013). These molecular pathways can induce GLUT-4 expression in skeletal muscles via the histone deacetylase 4/5-myocyte enhancer factor-2 (HDAC4/5-MEF2) axis and histone acetylation of GLUT-4 promoter by MEF2-GLUT4 enhancer factor (GEF) interactions leading to an increased GLUT-4 transcription (Richter & Hargreaves, 2013). Niu et al. (2017) also evaluated the role of HDAC4/5 in GLUT-4 expression and suggested that AE improves GLUT-4 transcription by inactivation of HDAC4/5 in skeletal muscles. AE is a potent inducer for GEF resulting in increased GLUT-4 expression so improving glycemic control (McGee & Hargreaves, 2006). Cunha et al. (2015) demonstrated that AE increases GLUT-4 content in muscles and reduces glucose concentration through a rise in glucose demand in diabetic animals. Hall et al. (2013) showed that daily AE by treadmill significantly increases GLUT-4 expression in gastrocnemius muscles and reduces insulin requirements for glucose regulation in diabetic animals. Muscle contraction during AE induces GLUT-4 translocation from the cytosolic pool to the cell membrane (Bergouignan et al., 2016). This contraction-induced glucose uptake through AE has been shown in athletes, is independent of insulin and may act through several pathways such as AMPK, sarcoplasmic Ca^{2+} , CaMK-I, and CaMK-II signaling pathways, changes in the AMP:ATP ratio and ATP turnover, Ras-related C3 botulinum toxin substrate 1 dependent signaling and mechanical stress-activated pathways (Jensen et al., 2014; Lauritzen, 2013; Lundell & Krook, 2013; Sylow et al., 2016; Sylow, Møller, Kleinert, Richter, & Jensen, 2014). Park, Park, Kim, Yoon, & Kim (2015) showed that cyclic ADP-ribose/nicotinic acid adenine dinucleotide phosphate and calcium second messengers are the main players for contraction-dependent GLUT-4 localization in the plasma membrane of T2D patients. Thus, it seems that upregulation of GLUT-4 in the cell membrane is affected by AE to improve glycemic control with a reduction of insulin resistance.

3.3 | AE and oxidative stress

Free radical overload known as oxidative stress is an important cause of insulin resistance and T2D (Yaribeygi, Butler, Barreto, & Sahebkar, 2018; Yaribeygi, Farrokhi, et al., 2018), and oxidative damage affects β cell function (Tangvarasittichai, 2015; Yaribeygi, Farrokhi, et al., 2018). Acute exercise increases free radicals but long-term AE significantly reduces oxidative stress and improves the redox state (Park & Kwak, 2016; Roque et al., 2013; Shi et al., 2007). The reduction of oxidative stress improves insulin sensitivity (Roque et al., 2013) that has been shown in athletes (Park & Kwak, 2016). Medeiros et al. (2015) demonstrated that AE improves insulin sensitivity by a reduction of oxidative damage in T2D.

3.4 | AE and ceramide level

There are some metabolites and biochemical compounds that are detrimental to IST such as free fatty acids and ceramides (Sears &

Perry, 2015; Shi et al., 2006; Summers, 2006). AE consumes free fatty acids as its metabolic substrate and reduces their serum levels of trained subjects (Hayashino et al., 2014) leading to improved insulin signaling and increasing insulin sensitivity (Boden & Shulman, 2002; Sears & Perry, 2015). Ceramides are a class of sphingolipid molecules that are present in the lipid bilayer membrane of eukaryotic cells and are important in many intracellular pathways such as free radical production, inflammatory responses, apoptotic processes, and modulation of genes expression (Kummarapurugu, Zheng, Rubin, Voynow, & Karandashova, 2017; Scheiblich et al., 2017; Senkal et al., 2017). It has been shown that ceramides impair IST resulting in insulin resistance and T2D (Galadari, Rahman, Pallichankandy, Galadari, & Thayyullathil, 2013; Kasumov et al., 2015a). Higher levels of ceramides have been shown to reduce insulin signaling by several molecular mechanisms such as β cells apoptosis, induction of inflammatory responses, endoplasmic reticulum stress, higher adipokine expression, oxidative stress, insulin resistance in peripheral tissues, and reducing insulin expression in islet cells (de la Monte et al., 2010; Galadari et al., 2013). In addition, these studies demonstrated that ceramide levels in obese subjects were higher than those who were lean, with the recommendation of weight loss to reduce ceramide synthesis (Dube et al., 2011; Fucho, Casals, Serra, & Herrero, 2016; Kolak et al., 2007). Thus, the decrease in plasma ceramide levels is commonly linked to enhanced insulin signaling and increased insulin sensitivity in peripheral tissues (Reali et al., 2017) and improved glucose homeostasis (Reali et al., 2017).

Kasumov et al. (2015b) reported that AE-dependent improvement of IST was related to reduced ceramide plasma levels in obese subjects, and Dube et al. (2011) observed that AE-dependent weight loss significantly improves insulin sensitivity by lowering ceramide levels in obese adults. Other studies have found that AE reduces plasma levels of ceramide, resulting in improved insulin signaling and reducing insulin resistance (Dubé et al., 2008; Hoy et al., 2009). It has been suggested that AE reduces ceramide levels by increasing fatty acid oxidation within muscles with a shift in *de novo* ceramide synthesis toward triacylglycerol formation (Dube et al., 2011).

3.5 | AE and diacylglycerol IRS-1 phosphorylation

AE may also be exerting its IST-inducing effects directly (Koval et al., 1999). Koval et al. (1999) demonstrated that AE directly induces insulin sensitivity by decreasing IR tyrosine phosphorylation that effectively improves IST in myocytes. IRS-1 upregulation is other possible pathway by which AE ameliorates IST and increases insulin sensitivity (Sanchez-Lopez et al., 2016). This receptor molecule is activated by the IR tyrosine kinase and then phosphorylates and activates Akt; thereby promoting glucose to enter into the cells via GLUT-4 transporters (Sanchez-Lopez et al., 2016). AE can markedly upregulate IRS-1 (De Matos et al., 2014) through upregulation and activation of IRS-1 modulators, phosphorylating the key protein

kinase of Akt and thereby improving IST leading to increased insulin sensitivity in insulin-dependent tissues (Bird & Hawley, 2017; Jorge et al., 2011; Kirwan et al., 2000; Ropelle et al., 2006).

3.6 | AE and β cells function/mass

AE can improve β cell function and prevent islets apoptosis (Almeida et al., 2012; Ghorbanzadeh, Mohammadi, Mohaddes, Dariushnejad, & Chodari, 2017). Ghorbanzadeh et al. (2017) demonstrated that AE downregulated p53 protein and decreased apoptosis, glucose, and HbA1c concentrations in diabetic rats. Piao et al. (2017) showed that 28 weeks of AE significantly reduced β cells destruction and ameliorated glucose metabolism in diabetic rats. In addition, there is evidence indicating β cell protective effects of AE (Slentz et al., 2009) suggested by aerobic physical activity improving β cell function and an increase in glucose-induced insulin secretion in islets of diabetic animals (Almeida et al., 2012). A recent randomized controlled trial showed that 12 weeks of AE improved insulin sensitivity and pancreatic islet cell function in overweight or obese male adolescents (Shih & Kwok, 2018). Moreover, Slentz et al. (2009) found that 8 months of AE can ameliorate β cell function by increasing the disposition index in overweight adults. However, a randomized controlled trial conducted in 2012 reported that whilst AE improved insulin sensitivity and reduced HbA1C, there was as no significant effect on β cell function (Bacchi et al., 2012).

3.7 | AE and capillarization

AE may indirectly improve insulin sensitivity by the induction of angiogenesis leading to the increase of capillary density and the growth of new vasculature networks (Prior, Blumenthal, Katzel, Goldberg, & Ryan, 2014). This physiological mechanism occurs in response to the demand for oxygen and metabolic substrates, and clearance of metabolic products (Prior et al., 2014). Nassis et al. (2005) found that AE increased insulin sensitivity without any change in body weight and independent of inflammatory parameters in overweight and obese girls. Also, Prior et al. (2014) observed that 6 months of AE ameliorated insulin sensitivity via an increase in muscular capillary density in adults with impaired glucose tolerance. They also reported in 2015 that AE-induced skeletal muscle capillarization resulted in the improvement of insulin sensitivity in older adults (Prior et al., 2015).

4 | OTHER POSSIBLE PATHWAYS

AE may modulate mitochondrial activity/biogenesis and in turn, affect β cells as well as skeletal muscle leading to the improvement of glucose homeostasis (Hood, Uguccioni, Vainshtein, & D'souza, 2011; Margolis & Pasiakos, 2013). It has been suggested that AE may induce changes in the transcription factors involved in IST molecular pathways (Masi et al., 2016; Wu, Wang, Jiao, Yue, & Wang, 2017). Dube et al. (2011) revealed that AE decreased insulin resistance through the reduction of diacylglycerol levels, which in turn increased insulin sensitivity.

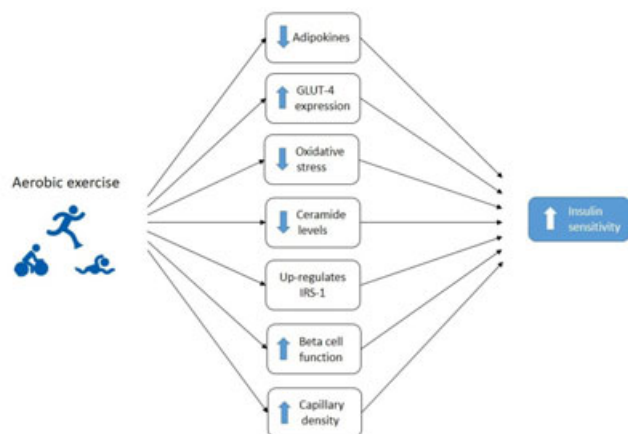


FIGURE 1 Aerobic exercise increases insulin sensitivity in peripheral tissues, leading to improved glucose homeostasis and a reduction in insulin resistance through at least seven different molecular mechanisms. GLUT-4: glucose transporter 4; IRS: insulin receptor substrate [Color figure can be viewed at wileyonlinelibrary.com]

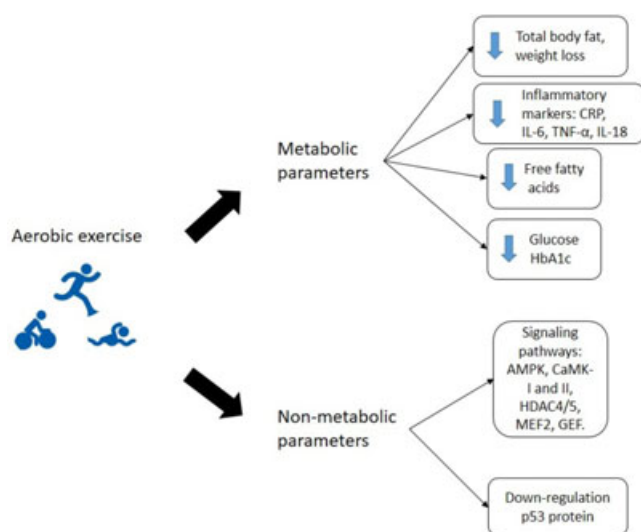


FIGURE 2 Mechanism of action of aerobic exercise on metabolic and nonmetabolic parameters. AMPK: AMP-activated protein kinase; CaMK-1: Ca^{2+} /calmodulin-dependent protein kinase II; CRP: C-reactive protein; GEF: GLUT-4 enhancer factor; HDAC4: histone deacetylase 4; IL-6: interleukin-6; MEF2: myocyte enhancer factor-2; TNF- α : tumor necrosis factor α [Color figure can be viewed at wileyonlinelibrary.com]

5 | CONCLUSION

The available data suggest that AE increases insulin sensitivity in peripheral tissues, leading to improved glucose homeostasis and a reduction in insulin resistance through at least seven different molecular mechanisms (Figure 1). AE can upregulate GLUT-4 and increase its density in insulin-dependent cell membranes; additionally, AE may also improve insulin sensitivity by a reduction in adipokines; AE improves oxidative stress-induced insulin

resistance by normalizing the redox state. In addition, improvement of β cell function, modulation of IRS-1 phosphorylation, lowering of ceramide plasma levels, and induction of angiogenesis are other molecular mechanisms by which AE improves IST leading to increased insulin sensitivity and enhanced glucose metabolism that may lead to a lower incidence of diabetic complications plus other metabolic and nonmetabolic effects (Figure 2).

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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