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Facultat de Farmàcia i Ciències de l'Alimentació

Departament de Bioquímica i Fisiologia

EXERCICI FÍSIC I RESISTÈNCIA A LA INSULINA ASSOCIADA A L'OBESITAT

Aina Ortigosa Laguna

Nutrició Humana i Dietètica

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Resum

Hi ha hagut un augment recent de l'obesitat poblacional, i es preveu que el percentatge de persones amb aquesta patologia augmenti en els pròxims deu anys. En un estat d'obesitat hi ha una disfunció en la via de senyalització de la insulina i es genera resistència a aquesta hormona. La insulina regula el metabolisme energètic promovent la captació i l'emmagatzematge de glucosa. La resistència a la insulina és la conseqüència de la inhabilitat de la insulina d'activar la senyalització de l'hormona i la consegüent regulació metabòlica. Són diferents mecanismes els que indueixen aquesta resistència a la insulina durant l'obesitat: la disfunció mitocondrial i l'estrès oxidatiu, l'estrès del reticle endoplasmàtic, la inflamació i l'autofàgia. L'exercici físic regular, especialment la combinació d'exercici aeròbic i de força, millora la sensibilitat a la insulina. També ho fa la AMPK, que és induïda per l'exercici físic i per fàrmacs. És a dir, l' exercici físic és una eina essencial en la prevenció i el tractament de la resistència a la insulina associada a l'obesitat. L'objectiu d'aquesta revisió és definir els mecanismes pels quals l' exercici físic es pot fer servir com a eina terapèutica per millorar la resistència a la insulina associada a obesitat.

Paraules clau: Resistència a la insulina, obesitat, exercici físic, estrès oxidatiu, disfunció mitocondrial, estrès del reticle endoplasmàtic, inflamació i autofàgia

Identificació i reflexió sobre els objectius pel desenvolupament sostenible (ODS):

Aquesta recerca bibliogràfica evidencia els beneficis de l'exercici físic, que serveixen com a una eina terapèutica pels individus que pateixen patologies metabòliques com l'obesitat i la diabetis mellitus tipus 2. Concretament, és l'exercici físic prolongat i de resistència el que millora els mecanismes que agreugen les disfuncions metabòliques associades a aquestes malalties, com ho és la resistència a la insulina. Els resultats aconseguits engloben l'assoliment de **l'ODS 3 "Salut i benestar"** que **"garanteix una vida sana i promou el benestar en totes les edats"**. El nombre de persones que pateixen tant obesitat com diabetis ha augmentat considerablement en els últims anys, igual que la xifra de mortalitat associada, a més d'una falta de diagnòstic i tractament. Amb les conclusions extretes del treball s'abasteix la meta **3.4** que té l'objectiu de **"reduir en un terç la mortalitat prematura per malalties no transmissibles mitjançant la prevenció i el tractament i promoure la salut mental i el benestar"**. Una investigació aprofundida sobre l'actuació beneficiosa de l'exercici físic davant de la reducció de la sensibilitat a la insulina pot donar unes pautes més concretes per aconseguir una prevenció i un tractament davant dels diferents mecanismes que provoquen resistència a la insulina.

Physical exercise and insulin resistance associated to obesity

Aina Ortigosa Laguna[1]

[1]University of Barcelona, Department of Pharmacy and Food Sciences, Barcelona, Spain

Correspondence: aortigla7@alumnes.ub.edu

There has been a recent increase in population obesity, and the percentage of people with this pathology is expected to increase in the next ten years. In a state of obesity, there is a dysfunction in the insulin signaling pathway and it is generated a resistance to this hormone. Insulin regulates energy metabolism by promoting the uptake and storage of glucose. Insulin resistance is the consequence of the inability of insulin to activate hormone signaling and the consequent metabolic regulation. Different mechanisms induce this insulin resistance during obesity: mitochondrial dysfunction and oxidative stress, endoplasmic reticulum stress, inflammation and autophagy. Regular physical exercise, especially the combination of aerobic and strength exercise, improves insulin sensitivity. So does AMP-activated protein kinase (AMPK), that it is induced by physical exercise and medication. In other words, physical exercise is an essential tool in the prevention and treatment of obesity-associated insulin resistance. The aim of this review is to define the mechanisms by which physical exercise can be used as a therapeutic tool to improve obesity-associated insulin resistance.

KEYWORDS

Insulin resistance, obesity, physical exercise, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, inflammation and autophagy

1 Introduction

Obesity is described as an excess of adipose tissue, it has a genetic basis and an important relationship with environmental factors, like the excess of calories in the intake and sedentarism or physical inactivity (1). It is a crucial risk factor in the appearance of metabolic alterations, associated with a generation of insulin resistance (IR) and the development of diabetes mellitus type 2 (DM2) (2–4). According to the study by Rogero Blanco et al. (5), 50% of obese individuals present IR. This IR manifests itself as a decrease in insulin's ability to regulate blood sugar, and is the pathological basis of multiple metabolic abnormalities. RI is the major metabolic defect that leads to DM2 due to a state of hyperglycemia (3–9). There has been a recent increase in obesity as a pandemic, and a concomitant increase in the prevalence of DM2, and it is expected that the percentage of people with these pathologies will increase in the next ten years, even a more complex situation if you take into account the high number of underdiagnosed diabetic population (4,6,10,11).

Physical exercise (PE) has proven to be a key tool in the prevention and management of both diabetes mellitus type 2 (DM2) and obesity, as well as other chronic non-communicable diseases, which the World Health Organization (WHO) considered a serious public health problem. In developed countries, these diseases and the metabolic comorbidities they involve, such as IR, are responsible for high morbidity and mortality and high social and health costs. It has been shown that regular physical activity programs

significantly reduce the mortality associated with these diseases, and the fact of increasing physical condition can improve the general state of health. This is how the implementation of regular PE programs and a healthy lifestyle appear as an alternative treatment and complete prevention of these metabolic diseases and leads to a decrease in the risk of developing RI. (2–4,6,11–13).

Despite the extensive evidence of the biological mechanisms that justify PE interventions, the benefits of this exercise and its impact on chronic non-communicable diseases remain unclear. Much research remains to be done on optimizing intervention patterns in terms of intensity, frequency and duration of exercise. Furthermore, it is essential to delve deeper into the mechanisms and factors that promote this IR and develop more effective and concrete prevention and treatment strategies (6,7). The objectives of this literature review are to update the current pathophysiology of metabolic dysfunctions such as IR. And mainly, to understand, define and discuss the complex adaptation mechanisms by which the application of PE acts as a possible non-pharmacological therapeutic tool against IR associated with pathologies such as obesity and DM2. To develop the review, articles published in the last fifteen years were examined, using *Pubmed* as a database and keywords such as "insulin resistance", "physical exercise", "AMPK", "oxidative stress", "mitochondrial dysfunction", "autophagy", "obesity" and "inflammation" were searched in both English and Spanish.

2 Insulin mechanism of action and signaling regulation

Under fasting conditions, to maintain normoglycemia, the alpha cells of the pancreatic islets secrete glucagon, a peptide hormone, responsible for stimulating catabolism, therefore the endogenous production of glucose (gluconeogenesis) in the liver, the main organ responsible for maintaining fasting glycemia (10). However, during feeding, especially after carbohydrate absorption, the β cells of these islets secrete insulin to counteract hyperglycemia (6,8,14) (Fig. 1).

Insulin is the main hormone responsible for controlling the uptake, utilization, and storage of nutrients. It is responsible for regulating the

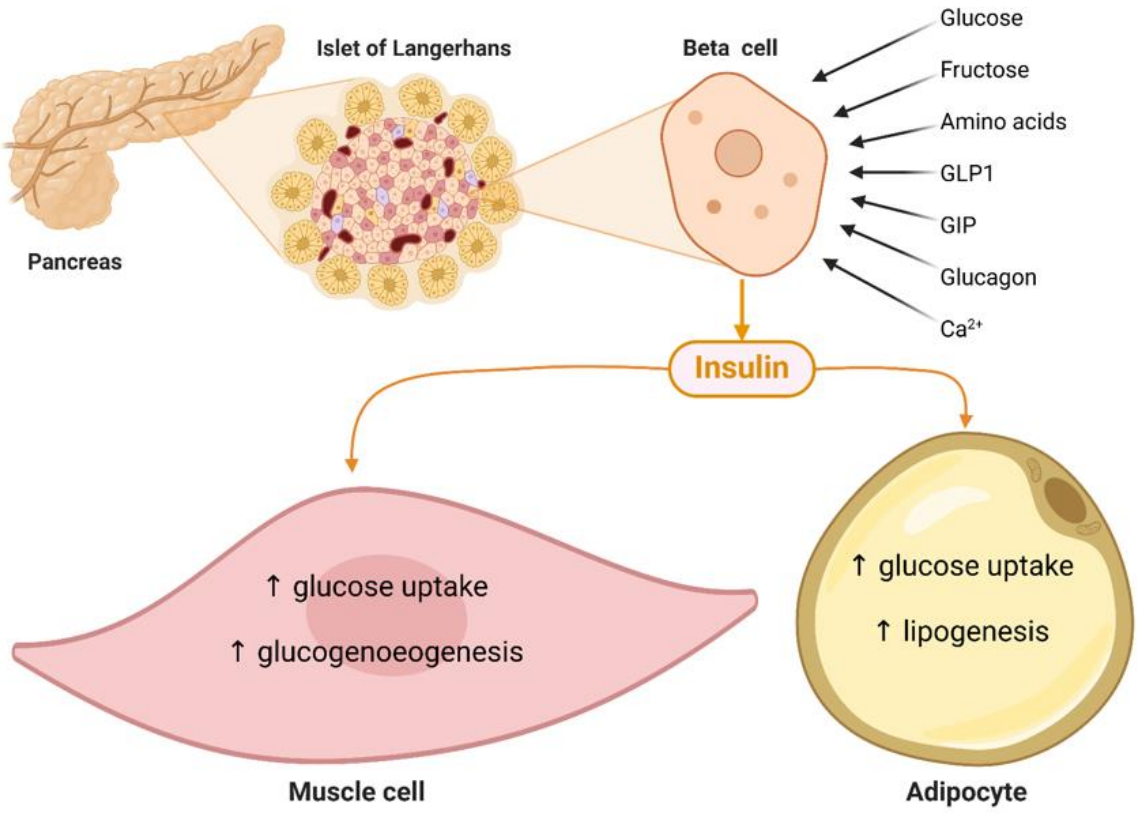

Figure 1. Mechanisms that induce insulin secretion in pancreatic beta cells and mechanisms of insulin action at the skeletal muscle and adipose tissue level. See text for more detailed description. Source: Own elaboration.

transport and absorption of glucose from the blood, mainly through the glucose transporter type 4 (GLUT4) (6,8,10,14). GLUT4-containing vesicles translocate to the plasma membrane after insulin stimulation to promote glucose uptake into the cell (15). It is mainly in skeletal muscle and adipose tissue where insulin promotes anabolism, therefore the conversion of glucose to glycogen (gluconeogenesis) and plasma fatty acids (FA) to triglycerides (lipogenesis), respectively (Fig. 1). In the liver, insulin inhibits gluconeogenesis, glycogenolysis, and ketogenesis. In addition, insulin's anabolic functions also include the promotion of protein synthesis in different tissues (6,8,10,14).

Insulin secretion into the portal circulation is induced by various stimuli, the main one being hyperglycemia, but it is also known that glucagon, fructose, amino acids and hormones such as incretins, some examples are glucagon-like peptide (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) promote insulin secretion (Fig. 1), while other substances, such as leptin and corticosteroids, inhibit it (6). In addition, Ca^{2+} promotes the initiation and fusion of insulin precursor granules to the plasma membrane of pancreatic β cells in the insulin secretory pathway, facilitating subsequent insulin secretion (16). In addition to stimulating hormone secretion, many of these stimuli also promote its gene expression (6).

The biological actions of insulin are initiated when it binds to its receptor, an integral membrane glycoprotein formed by two α and two β subunits, linked through disulfide bridges. The α subunit contains the insulin binding site, and is completely extracellular. The β subunit is composed of an extracellular domain, a transmembrane domain, and an intracellular domain. The binding of insulin to the α subunit of the receptor generates conformational changes that induce tyrosine kinase activity of the intracellular domain in the β subunit of the receptor, causing its autophosphorylation. Phospho-tyrosine residues are recognized by different adaptor proteins, including those of the insulin receptor substrate family (IRS1) (Fig. 2.A). IRS1s are the main mediators of insulin's metabolic actions and function by organizing molecular complexes that trigger intracellular signaling cascades (6,14).

Insulin has two main signaling pathways. On the one hand, the MAPK/ERK1 pathway, which regulates insulin-associated gene expression, since this hormone is a potent growth factor. The ERK1 kinase is necessary for adipogenesis, suggesting the participation of this pathway in the actions of insulin (8,14). An inhibition or decrease in this cascade can lead to decreased or altered adipogenesis, which may explain the development of IR (17). On the other hand, the insulin signaling pathway PI3K/Akt is responsible for most of the metabolic actions of the hormone (6,8,14). Phosphatidylinositol-3-kinase (PI3K), after being recruited to the membrane by IRS1 phosphorylated on tyrosine residues, converts phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3), which activates pyruvate dehydrogenase kinase (PDK) (15), resulting in the phosphorylation, and concomitant activation of protein kinase B (Akt). Activation of this pathway promotes glucose uptake in skeletal muscle and adipose tissue through the translocation of GLUT4 from intracellular compartments to the cell membrane (Fig. 2.A). In addition, Akt participates in protein, lipid, and glycogen synthesis through the phosphorylation and inhibition of glycogen synthase kinase 3 beta (GSK3β) (6,8,14,15).

There are two mechanisms that define the scope and duration of the insulin signal, and therefore regulate its metabolic actions. One is autoregulation or homologous regulation, where enzymes activated by the insulin pathway itself inhibit the activity of key insulin signaling proteins. The other is heterologous regulation, where molecular mechanisms unrelated to those activated by insulin also inhibit insulin signaling. Different regulatory mechanisms have been identified at the level of the receptor, IRS1 and proteins located downstream of both, including PI3K, Akt and GLUT4 (8).

According to Gutiérrez-Rodelo (8) several studies have shown that the activity of the insulin receptor and IRS1 is regulated by the action of phosphatases such as phosphor-tyrosine phosphatase 1B (PTP1B), which dephosphorylate specific tyrosine (Tyr) residues of the active insulin receptor, thereby reducing its activity. Another key mechanism is the phosphorylation of serine/threonine (Ser/Thr) residues of IRS1, by protein kinases such as protein kinase C or PKC, protein kinase A or PKA, and MAPKS such as c-Jun amino-terminal kinase (JNK). Ser/Thr phosphorylation sites are located close to the interaction domain of IRS1 with the insulin receptor, which could affect the conformation of the receptor or the access to Tyr residues, thus decreasing its phosphorylation, and consequently, the activation of the pathway. Various agents such

as proinflammatory cytokines, FA, ceramides, amino acids, angiotensin II and hyper-insulinemic states increase the activity of these kinases. There are also suppressor proteins of cytokine signaling proteins (SOCS), which are potent repressors of the insulin signaling pathway, whose expression is induced by the action of insulin in different tissues. They interact directly with both, the insulin receptor and IRS1, when they are active, and inhibit IRS1 Tyr phosphorylation by competing for the same interaction site, which promotes IRS1 degradation and inhibits insulin receptor kinase activity. In addition to regulation at the level of the insulin receptor and IRS1, there are regulatory points below both proteins that also influence the modulation of the insulin signal. For example, lipid phosphatases do so by modulating PIP3 levels; Both phosphatase and tensin homolog (PTEN) and SH2-containing inositol phosphatase 2 (SHIP-2) dephosphorylate PIP3, thereby specifically antagonizing Akt signaling (8,18) (Fig. 2.B). In addition, the impediment of the Akt signaling pathway also triggers the dephosphorylation and consequent activation of GSK3β, which helps in the induction of apoptosis of pancreatic β cells and leads to a decrease in insulin secretion resulting in an increase in IR (16).

In conclusion, different mechanisms lead to this decrease in Tyr phosphorylation, both of the insulin receptor and IRS1, which lead to a decrease in PI3K activity (and its degradation) and, therefore, to a decrease in Akt phosphorylation and the consequent IR. Gutiérrez-Rodelo (8) mentions the importance of the increase in the phosphorylation state of IRS1 proteins in clinical studies carried out with obese patients, where IRS1 expression decreases by around 54%.

3 Obesity-associated insulin resistance mechanisms

Hyperglycemia is thought to develop when there is an excess of nutrients and normal insulin secretion is not sufficient to return to normoglycemia. This promotes stress on the pancreas because the pancreatic β cells secrete more insulin in an effort to keep circulating glucose within the normal range, a process known as compensatory hyperinsulinemia. If this IR persists over the years, the pancreas becomes "exhausted" to the point of generating little or no insulin due to an exhaustion of the β cells, which results in sustained hyperglycemia. This situation is known as pancreatic failure and is a characteristic of DM2. IR is a characteristic feature of metabolic dysfunction induced, among other causes, by obesity (3,8,10,12,19), pathology that also contributes significantly to the development of other conditions, such as dyslipidemia, hypertension and atherosclerosis (3,8,10). At a molecular level, IR is the consequence of insulin's inability to effectively activate IRS1, the consequent hormone signaling and the metabolic responses mentioned above, thus contributing even more to hyperglycemia, in addition to a decrease in glucose uptake by cells of metabolic tissues, such as adipose, liver and muscle, due to a dysfunction of GLUT4 (6,8,10,14).

IR can be diagnosed using dynamic tests, simple indices and biochemical markers, relatively simple tests of fasting blood glucose and insulin levels, the glucose tolerance test, the HOMA-IR index, glycated hemoglobin (HbA1c), the IR index and biological indicators such as determination of serum levels of leptin, adiponectin, triglycerides,

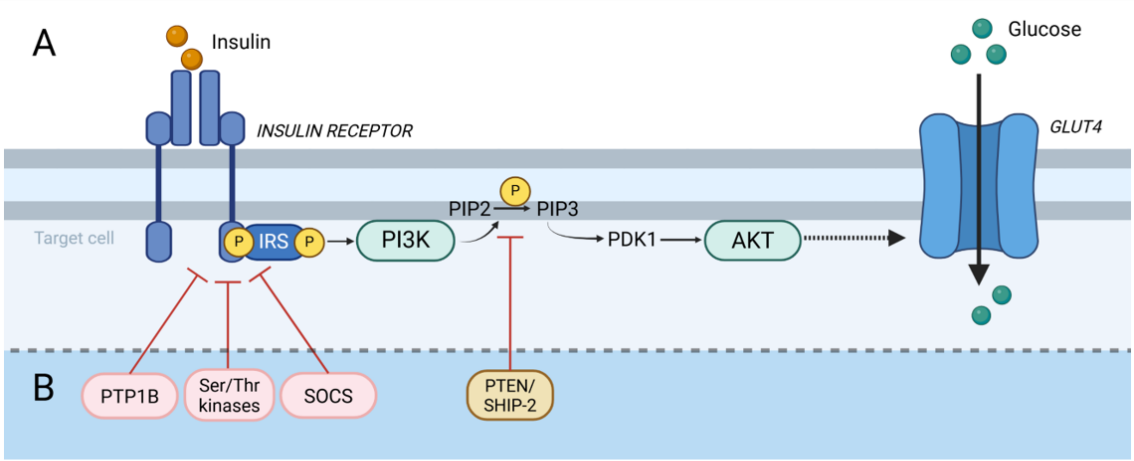

Figure 2. (A) Activation of the PI3K/Akt signaling pathway by insulin leading to GLUT4 translocation. (B) Mechanisms of negative regulation of the P13K/Akt signaling pathway at the level of the receptor, IRS, and downstream proteins. See text for more detailed description. Source: Own elaboration.

high-density lipoprotein and cholesterol, to make relevant predictions and judgments (14).

Several extrinsic and intrinsic cellular mechanisms have been identified that present a cause-effect relationship between weight gain and peripheral IR. Intrinsic cellular pathways include autophagy, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum (ER) stress, while metabolic tissue inflammation (metaflammation) and hyperinsulinemia are extrinsic mechanisms. (8,14,20) (Fig. 3).

3.1 Oxidative stress and mitochondrial dysfunction

Under physiological conditions, there is a state of equilibrium in the redox balance resulting from the functional interaction between oxidant and antioxidant agents. However, when the redox balance is lost due to increased generation of reactive oxygen species (ROS), oxidative stress (OS) occurs (10). Although moderate concentrations of ROS are required for normal

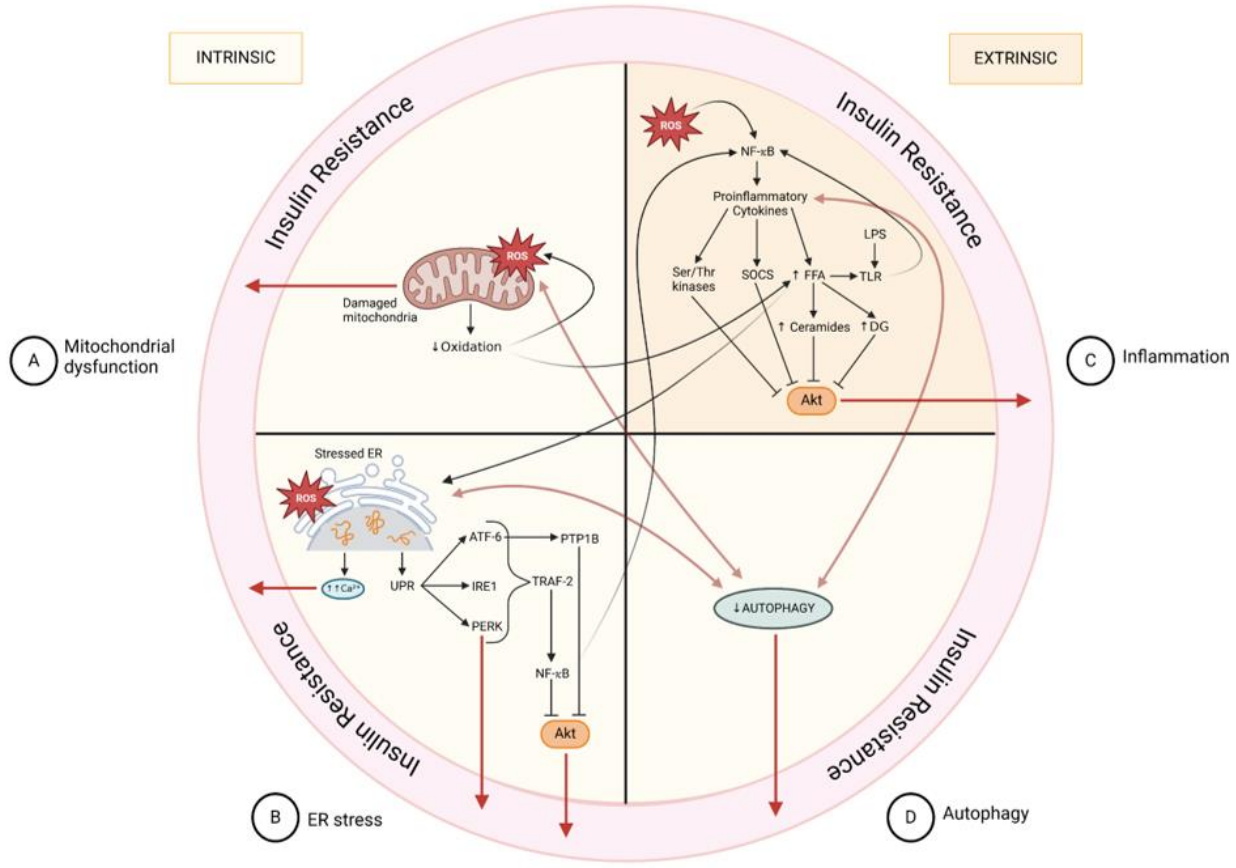

Figure 3. Diagram of the mechanisms that present a cause-effect connection with insulin resistance. (A) Mechanism by which oxidative stress and mitochondrial dysfunction lead to insulin resistance. (B) How endoplasmic reticulum stress leads to insulin resistance. (C) Different mechanisms by which inflammation leads to insulin resistance. (D) Decreased autophagy induces insulin resistance. See text for more detailed description. Source: own elaboration

intracellular signaling, excessive levels of ROS can induce activation of proinflammatory pathways, ER stress, and alterations in mitochondrial genes, which is related to mitochondrial dysfunction (2,6,8,14,18) (Fig. 3). In DM2 linked to overweight and obesity, an increase in the state of chronic OS is observed, induced by macrophage infiltration in adipose tissue. IR is a harmful effect caused by altered levels of ROS, since they negatively affect both the release of insulin by pancreatic β cells and the sensitivity of this hormone in peripheral tissues (8,14). Current evidence suggests that decreasing pro-oxidant factors or increasing antioxidant factors should be considered in the treatment of DM2 (10).

The mitochondria is a cellular organelle that plays an important role in energy metabolism, and is responsible for providing most of the necessary energy in the form of adenosine triphosphate (ATP) from organic molecules that are oxidized in the presence of oxygen via catabolism (8,14). According to Gutiérrez-Rodelo (8) mitochondrial dysfunction can be defined as the result of a

reduction in mitochondrial protein content and/or a decrease in the activity of the enzymes that participate in the oxidative process, and a decrease in the oxidation of substrates (carbohydrates and lipids) that affects the flow of electrons, causing a leak of these towards oxygen forming ROS (Figure 3.A). This causes various damages at the mitochondrial and cellular level, such as a decrease in the biogenesis of this organelle and mitophagy, that is, the elimination of damaged mitochondria, and therefore a decrease in the number of mitochondria (8,14). Mitochondrial dysfunction leads to lipid accumulation in non-adipose tissues such as skeletal muscle, liver, and pancreatic β cells and to the development of IR (17,18) (Fig. 3.A). It is noteworthy that, controversially, recent evidence indicates that mitochondrial dysfunction is rather the result of IR itself rather than its cause (8). That is to say, IR does not arise when the mitochondrial electron transport chain is interrupted, but rather, it is IR that leads to deterioration of mitochondrial function and quality (14).

3.2 Endoplasmic reticulum stress

The ER is an organelle that contributes to cellular homeostasis, playing a central role in cell death and survival signaling (19,21). It performs important cellular functions, such as intracellular calcium storage (8), the biosynthesis of lipids and proteins, including the assembly, folding and storage of the latter, and the regulation of enzymatic activity and metabolism (8,18,19,21). The demand on the ER may increase, leading to an overload of its functional capacity and a deterioration in protein folding and calcium depletion in this reservoir (8,14,21), this overload is known as ER stress. It occurs under conditions of cellular stress such as obesity-induced inflammation, a ROS increase, a situation of overfeeding, during nutrient deficiency, in a condition of physical inactivity, and in Ca^{2+} disorders (8,14,18,21). In an overfeeding situation there is an accumulation of FA in skeletal muscle that accelerates ER stress, since the lipid composition modulates protein folding in the ER, inhibits the function of calcium-dependent enzymes and chaperones and alters ER calcium homeostasis (12) (Fig. 3.B).

On the one hand, as mentioned above, in the pancreatic beta cell, Ca^{2+} has a promoting effect on insulin secretion. However, sustained ER stress (which happens during an obesity state) alters ER calcium homeostasis, decreasing ER calcium content while increasing cytoplasmic Ca^{2+} levels, and excessive calcium signaling is detrimental to these cells and ultimately inhibits insulin secretion (16). On the other hand, as a compensatory mechanism to stress and specifically to protein misfolding, the unfolding protein response (UPR) is activated in the same organelle. This is mediated by signaling pathways through three sensors bound to the ER membrane, we are talking about the reticulum protein kinase (PERK), the transcription activator factor 6 (ATF-6) and the endoribonuclease kinase 1 (IRE1). Under normal conditions, these transmembrane proteins bind to the BiP protein or binding immunoglobulin protein, which is a molecular chaperone that inhibits them. However, when ER stress occurs, it dissociates from the three sensors and allows them to initiate the UPR (16,19). The UPR allows the restoration of homeostasis of ER functions by inhibiting protein synthesis and increasing protein degradation and the expression of genes encoding chaperones (8,16,19,21).

The PERK signaling pathway, which acts by phosphorylating eIF2α, decreases protein synthesis by reducing protein load in the ER lumen (19,21). However, continued ER stress can decrease PERK/eIF2α pathway activity in β cells and alter proinsulin structure, triggering proinsulin misfolding and consequently leading to insufficient insulin secretion, causing hyperglycemia and pancreatic beta cell apoptosis, which can lead to IR (16,19,21). On the other hand, ATF-6 allows the activation of the synthesis of chaperones that block protein synthesis and decrease protein folding capacity (8,19), but in a state of chronic stress, ATF-6 increases the expression of PTP1B, which contributes to the inhibition of Akt and the consequent IR (16). Finally, the three ER stress sensors (PERK, ATF-6 and IRE1) induce specific inflammatory responses when they interact with TNF receptor-associated factor 2, also known as TRAF-2, and as explained below it activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and consequently JNK, resulting in the inhibition of the Akt pathway and in an increase of IR (8,10,16,19,22) (Fig. 3.B).

Another possible mechanism of IR is the inhibition of the transfer of newly synthesized insulin receptors to the cell surface due to ER stress (14). Gutiérrez-Rodelo et al.(8) claim that this ER stress condition has been detected in the adipose and

liver tissue of obese humans, which was reversed in patients undergoing weight loss surgery (8).

3.3 Inflammation

Obesity is defined as the presence of an excessive amount of body fat or adipose tissue that is manifested by an increase in body weight. In the state of obesity there is an increase in the accumulation of lipids, which causes an increase in the size of fat cells, and therefore the expansion of adipose tissue. In addition, the infiltration of immune system cells such as macrophages into adipose tissue also increases. All these alterations in this tissue due to obesity give rise to inflammation, which is a physiological response to protect the body and it is characterized by the increase in adipokines and proinflammatory cytokines, and the secretion of free fatty acids (FFA) (2,14). Chronically increased levels of inflammatory factors induce and aggravate numerous diseases, and several studies have highlighted it as an important promoter of IR and systemic metabolic dysfunction (2,14,23,24).

ER stress and the subsequent UPR initiate the inflammatory cascade by activating TRAF-2 and the IKK complex, which phosphorylates and ubiquitinates Iκβ (an inhibitor of NF-κB), resulting in the degradation of Iκβ and subsequent nuclear translocation and activation of NF-κB. The production of ROS has also been reported to cause the activation of NF-kB. Once activated, NF-κB promotes a state of chronic inflammation in liver and muscle tissue by regulating the induction of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α (8,10,19,22). Proinflammatory cytokines activate Ser/Thr kinases such as JNK, IKKβ and PKC, in addition to the expression and activation of SOCS, which results in decreased IRS1 expression, altering the PI3K/Akt pathway, ultimately leading to IR (6,8,10,14,19,22) (Fig. 3.C).

Another important factor in obesity-associated inflammation is the activation of toll-like receptors, also known as TLRs, particularly TLR-2 and TLR-4. TLRs are a family of receptors that participate in the innate response of the immune system (they are found at elevated levels in muscle and adipose tissue in obesity conditions), and are generally activated by molecular patterns associated with pathogens such as lipopolysaccharide (LPS) and saturated dietary FA.

There is evidence that the activation of TLRs promotes the synthesis and secretion of proinflammatory cytokines through the NF-kB pathway in a positive feedback mechanism. The action of TNF-α and IL-6 stimulates hormone-sensitive lipase and favors the lipolysis of triglycerides stored in these tissues, which increases the release of FFA and produces lipotoxicity. Although the exact mechanism that leads to IR is not known with certainty, one of the most important theories is related to lipotoxicity (6). Excess circulating FFA in obesity conditions is accompanied by an increase in diglycerol (DG) and ceramides (2,8). DG promotes PKC activation (2), which phosphorylates and inhibits the insulin receptor, and ceramides activate protein phosphatase 2A or PP2A, which dephosphorylates and inactivates Akt, inhibiting the insulin signal, in addition to decreasing lipolysis (6,8) (Fig. 3.C). In this context, studies performed in mice with decreased TLR expression show that these animals are protected from the development of obesity and IR (8).

3.4 Autophagy

Autophagy or “self-feeding” is a recycling mechanism responsible for maintaining cell metabolism and survival, and energy homeostasis. It acts in defense against various types of stress, such as oxidative damage, by providing nutrients to cells and degrading toxic molecules such as misfolded proteins, damaged organelles (including damaged mitochondria in mitochondrial dysfunction), oxidized lipids and infectious agents, and transforms them into new resources, reducing cell death (18,24–26). This process counters the harmful effects of ROS and plays a vital role in the recovery of ER stress and dysfunctional or stressed mitochondria, inhibits the secretion of proinflammatory cytokines, and maintains the functionality of pancreatic β-cells (18,24). Consequently, impaired and dysregulated autophagy is associated with metabolic disorders (in insulin target tissues including liver, skeletal muscle and adipose tissue) such as fat accumulation, hyperglycemia, inflammation, IR and DM2 (14,24,25). Obesity, which is associated with OS and elevated FA concentrations, is characterized by an inhibition of autophagy due to a downregulation of the autophagy gene Atg7 in the liver and muscle, even in the adipose tissue

(which has a high expression of autophagy genes). This causes IR through increased ER stress, increased ROS that induce OS and oxidize the Atg4 gene, deactivating it. In addition to the production of proinflammatory cytokines such as IL-1β and TNF-α mediated by NF-κB that lead to increased inflammation (18,24,26,27) (Fig. 3.D). Paradoxically, muscle or liver specific inactivation of the Atg7 gene protects mice from obesity and IR by increasing the expression of fibroblast growth factor (FGF21), which improves IR by different mechanisms (18,26) that are explained below.

4 Physical exercise and life style influence on insulin resistance

PE is a widely recommended activity due to its multiple health benefits and is important for preventing and treating chronic diseases and speeding up recovery (7). PE may be a fundamental mechanism to prevent or improve IR and its metabolic complications, helping with glycemic control in diabetic patients (1,6,10,12,14). Regarding the type of exercise, there is no consensus on the best strategy (14).

On the one hand, regular exercise, especially strength training, increases skeletal muscle mass and quality by providing stimuli that result in muscle fiber hypertrophy, leading to improved physical condition and reduced mortality (6,11,14,28) (Fig. 4). Low insulin sensitivity has been associated with low muscle mass. On the other hand, aerobic or resistance exercise is characterized by the execution of continuous and cyclical movements that involve large muscle groups. It is found in modalities like walking, jogging, cycling, etc. Resistance training, and its chronic adaptation, as muscle mass accumulates, leads to an increase in basal metabolism, in other words, an increase in energy consumption (Fig. 4). A predominance of the oxidative catabolic pathway is reflected and great improvements have been observed in relation to the redox balance; both by an increase in the levels of antioxidant biomarkers and by a decrease in oxidation biomarkers in the blood (10). There is an improvement in the capacity for lipid oxidation and better glycemic regulation and control, increasing the uptake, transport and consumption of glucose in cells through glycolysis (10,11,14,28,29) (Fig. 4). These events occur independently of the action of insulin, thereby decreasing hyperglycemia, resulting in better IR (10,11,14,28,29). In acute exercise, these insulin-independent mechanisms that improve insulin resistance result from the recruitment of molecules related to cellular stress promoted by the process of muscle contraction such as those of the AMP-activated protein kinase (AMPK) signaling-dependent pathway (15) (Fig. 4).

In the study by Poblete-Aro et al. (10) no changes were observed in biomarkers related to OS and DM2 in individuals undergoing high-intensity strength exercises, while improvements were observed in those who did moderate-intensity aerobic exercises (10). However, in the study by León-Ariza et al. (6), it is true that with aerobic resistance exercises the HbA1c is reduced more than with strength exercises, but it has been seen that with a combination of both a reduction of this HbA1c up to three times greater is achieved (6,14). Their combined performance results in a lower occurrence of obesity-related risks such as DM2 compared to performing each type of exercise separately. It should be noted that moderate intensity could be more effective than high intensity exercise for greater use of intracellular lipids (6,11). Additionally, León-Ariza et al. (6) explain that at least after 6-8 weeks of training is when improvement in blood glucose and insulin levels is evident through laboratory tests. By continuing with the progression and intensity of the exercise, after three months, the function of pancreatic beta cells improves in people with DM2 (6). Besides, Shen et al. (14), state that a long-term aerobic exercise intervention (8-12 weeks) increases insulin sensitivity in sedentary overweight or obese individuals with insulin resistance (14). It has been shown that, in the long term, all have had an improvement in the parameters consulted (10).

In terms of a long-term effect, in the absence of training, it is estimated that muscle mass begins to decrease from the age of thirty, and the rate of decrease increases even more after the age of sixty. The basal metabolic rate also decreases, with muscle loss being the major contributor to this decrease. This reduction also increases the propensity to gain weight with age. Aging is associated with a risk of systemic inflammation, and an increased risk of developing IR and DM2.

Various pathophysiological changes in muscle aging, such as mitochondrial dysfunction, intracellular lipid accumulation, decreased maximum oxygen capacity, and increased inflammation, contribute to IR in muscle tissue. Nevertheless, PE can slow the rate of physiological decline associated with primary and secondary aging and provide clinical benefits. Expert athletes (who regularly train at high levels 4 to 5 times per week) have been shown to show minimal reduction in muscle mass with age, so physical exercise can sharply counteract the muscle atrophy observed among sedentary older adults (11).

During PE, skeletal muscle fiber requires additional amounts of substrates such as FA and glucose. In the case of glucose, muscle contraction generates (independently of insulin) a greater activation of molecules such as PI3K, and therefore, the Akt pathway (6,15), which promotes the translocation of GLUT4 to the plasma membrane (1,6,30). This results in a reduction in plasma glucose that is maintained over time and is beneficial for improving IR. In addition, when the Akt pathway is activated, the activation of GSK3β is reduced, thereby increasing glycogen synthesis (6). In the case of fats as an energy source, the contractile activity of physical

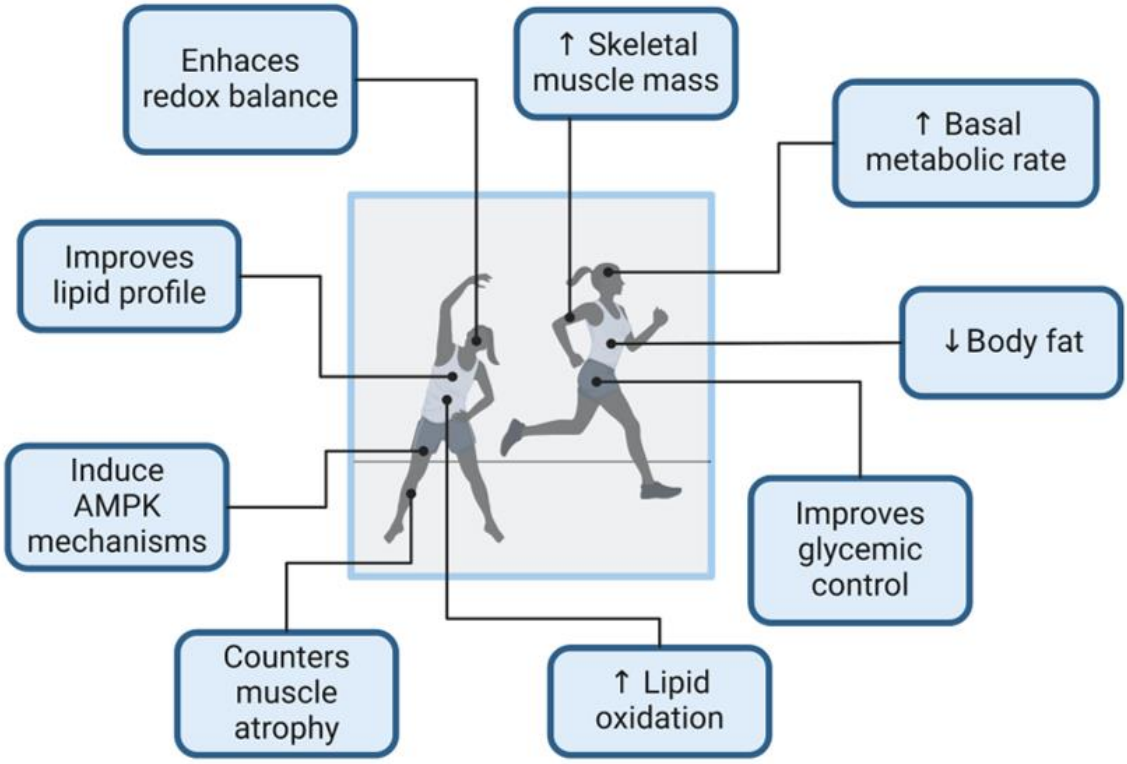

Figure 4. Diagram of the effects of physical exercise on the body related to insulin resistance relief. See text for more detailed description. Source: Own elaboration

exercise, especially resistance, increases their transport to the muscle. This process is similar to the one that occurs in a state of overfeeding. However, chronic physical activity also increases the oxidation of these lipids and prioritizes their storage to reduce the accumulation of lipid intermediaries such as ceramides and DG (4,6) (Fig. 4).

In developed societies, excessive caloric intake and a sedentary lifestyle are factors that lead to a prevalence of obesity, dyslipidemia and the development of IR and DM2 (1,7,12,19).

Therefore, not only low physical activity but also diet influences IR. In models of obesity induced by a high-fat diet, it has been shown that Tyr phosphorylation of the insulin receptor decreases due to an increase in phosphorylation at Ser-206 of IRS1 through JNK (3). Furthermore, in the study of Pauli et al. (7) PTP1B protein expression was seen to increase with the high-fat diet. But at 16 hours after acute exercise some reductions in PTP1B and JNK levels were observed in skeletal muscle (7). So we can say that this decrease in insulin signaling is alleviated by moderate aerobic exercise, although not at comparable levels of

exercise plus a low-calorie diet (1,3). Similarly, the combination of strength and/or aerobic training with dietary restrictions produced greater improvements in glucose tolerance than diet alone (28). Currently, physical exercise, dietary control and pharmacological interventions are the main accepted means to alleviate IR (14).

It is true that the reduction of adipose tissue related to abdominal obesity is related to improvements in metabolism and the decrease in the development of abnormalities of this metabolism (28). But it is important to mention that several studies have shown that aerobic physical exercise at a moderate intensity improves insulin sensitivity in diabetics in the absence of body weight changes (1). Therefore, the goal should not be weight loss, but rather to reduce the risks added to obesity such as this IR, dyslipidemia and diabetes among others (11).

5 AMPK pathway in the insulin resistance mechanism

AMPK is activated as a response to stress in the energy state such as that during exercise (30,31). Both exercise and electrically induced contractions in muscle have been shown to acutely increase AMPK activity in adipose tissue, liver, and skeletal muscle (30,32). Protein kinases that activate AMPK are calcium-calmodulin-dependent protein kinase β or CAMKKβ, which is activated by increases in intracellular Ca2+ without any significant change in ATP level, and liver tumor suppressor kinase B1 or LKB1, which is activated as a response to energy stress, such as that during exercise. LKB1-dependent AMPK phosphorylation is enhanced by AMP binding to AMPK, and at the same time, AMP binding inhibits AMPK dephosphorylation (33).

AMPK, through modulation of the transcription cofactor (PGC-1α), increases cellular ATP generation by promoting catabolic pathways such as the oxidation of FA and glucose (glycolysis), thereby promoting glucose transport and uptake into cells independently of insulin (15,25,33) and inhibits ATP-dependent anabolic pathways such as the synthesis of fatty acids, cholesterol, proteins and glucose from non-carbohydrate sources (25,32) (Fig. 5).

In addition to regulating metabolism, PE induced AMPK can favorably regulate systemic glucose homeostasis in skeletal muscle, but also in liver and adipose tissue and consequently, represent a feasible intervention to improve IR (3,10,14). These observations, together with epidemiological evidence that diabetes is less common in physically active individuals and the demonstration that regular exercise enhances systemic insulin action, suggest a central role for AMPK in regulating insulin sensitivity. In model systems, sustained decreases in AMPK activity accompany IR, and this has been conclusively demonstrated in adipose and muscle tissue from very obese individuals including some with DM2. A study by Ruderman et al. (32) demonstrates that AMPK activity is significantly decreased (30%–50%) in the adipose tissue of 75% of severely obese individuals who are insulin resistant (32).

AMPK negatively regulates factors that have been linked to IR, including inflammation, oxidative stress, and ER stress, and increases autophagy, and secondarily, mitochondrial function. In contrast, these cellular stressors, which activate each other, appear to decrease AMPK activity (16,30,32) (Fig. 5).

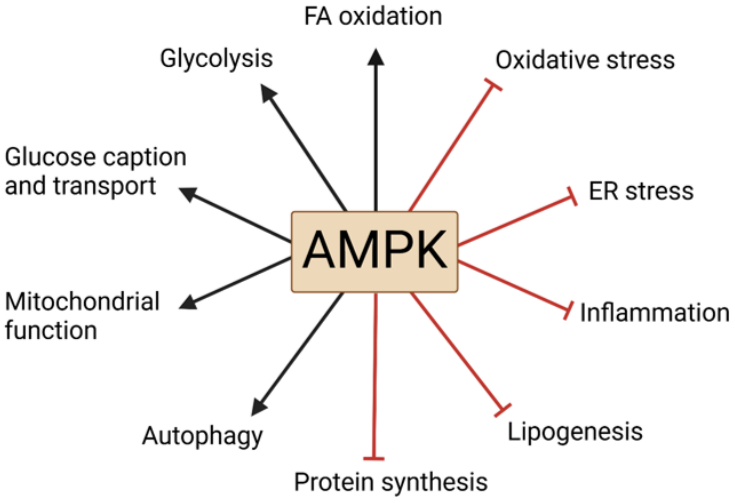

Figure 5. Diagram of the functions regulated by AMPK related to insulin resistance. The black and red arrows indicate the pathways that AMPK activates or inhibits, respectively. Source: Own elaboration

5.1 Physical exercise and AMPK contribution to oxidative stress and mitochondrial dysfunction

Physical activity is considered the dominant factor in the link between IR and mitochondrial respiration: regulating and controlling aerobic capacity may be essential to control the IR (14). For instance, Dietrich et al. (3) demonstrated in mice that exercise induces oxygen consumption and the expression of uncoupling protein 2 or UCP2, which is a mitochondrial protein that uncouples substrate oxidation from ATP synthesis, thereby allowing energy to be released as heat and reducing electron "leakage" and, therefore, ROS production (3,10,16) (Fig. 6.A). Exercise reduces ROS levels, and in the long term, specifically aerobic exercise, can improve the body's antioxidant system to control OS (14,16,21).

However, according to Shen et al. (14), in the last decade, various evidences have indicated that PE promotes the production of ROS mainly due to an increase in the excito-contractile activity of skeletal muscle. This phenomenon generates a transient redox imbalance called "exercise-induced oxidative stress" (14). ROS generated during exercise are beneficial as they induce adaptations that activate different signaling pathways through AMPK (34), which in turn converge in the activation of transcription factors such as Nrf2 through PGC-1α, which acts as a coactivator. After oxidative stimulation, they dissociate, allowing Nrf2 to increase mitochondrial biogenesis along with increased expression of antioxidant enzymes and decreasing levels of oxidative stress biomarkers (10,18) (Fig. 6.A). Therefore, the oxidation of fatty acids is promoted. There is evidence showing that the expression of PGC-1α in skeletal muscle is decreased in diabetics (34). It should be noted that in a state of obesity and IR, Nrf2 is inhibited by GSK3β (26).

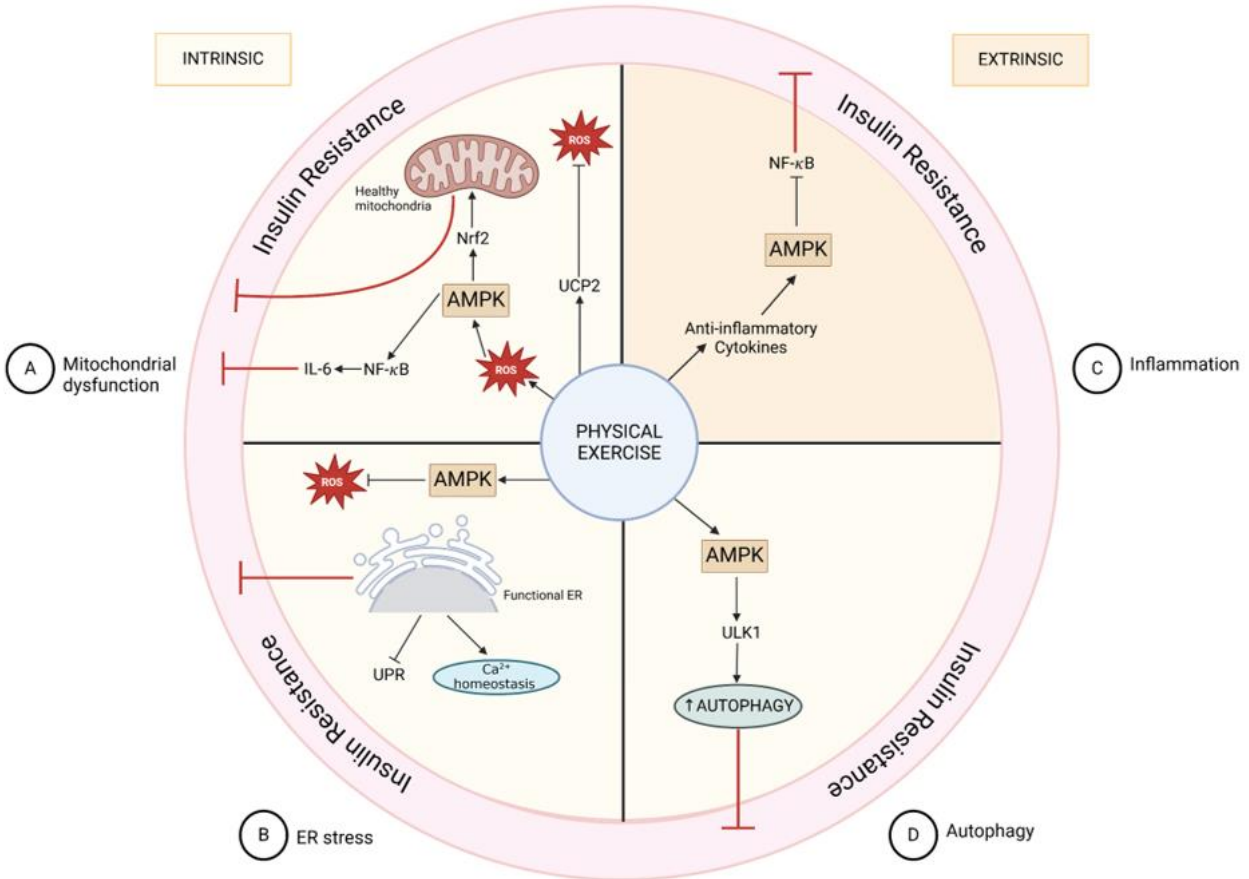

Figure 6. Diagram of the mechanisms by which exercise improves insulin resistance via AMPK. (A) How exercise reduces insulin resistance through improved mitochondrial function (B) Exercise prevents endoplasmic reticulum stress, which decreases insulin resistance. (C) Physical exercise reduces inflammation and, consequently, insulin resistance. (D) Exercise increases autophagy, which decreases insulin resistance. See text for more detailed description. Source: Own elaboration

On the other hand, these OS PE-induced ROS phosphorylate and activate the inhibitory protein Iκβ. Thus, NF-κB can induce the expression of cytokines such as IL-6, which in this context of physical activity acts as an anti-inflammatory protein (Fig. 6.A). Additionally, AMPK promotes an increase in tissue glutathione levels, which also acts as an antioxidant (10). In addition, ROS inhibit PTP1B and PTEN, thereby decreasing the downregulation of insulin signaling (14).

5.2 Physical exercise and AMPK contribution to RE stress

Numerous studies indicate that exercise could effectively improve several ER stress-related pathologies, such as obesity and diabetes. It has been found that the beneficial effect of exercise will depend on the modality and duration of exercise (12,19). Hong et al. (19), observed markers of ER stress in mice after bouts of physical activity. The initial response to aerobic training induces ER stress and activates UPR signaling (19). However, after prolonged physical training at a moderate intensity, these increased markers are alleviated, suggesting that activated UPR signaling is induced to acclimatize to physical training for cell survival and adaptation. An attenuation of ATF-6, PERK, eIF2α, inflammatory cytokines, NF-kB and JNK is observed. In addition, PE and the consequent activation of AMPK lead to a potentiation of the action of antioxidant defenses, preventing the establishment of OS, as one of those responsible for ER stress (16,19,21) and calcium imbalance (35) (Fig. 6.B).

De Sousa Fernandes et al. (21), observed that not only a decreased PE, but also an excess of it is detrimental to cellular homeostasis; When aerobic exercise promotes high demands of muscular work, it leads to conditions of exhaustion and voluntary motor failure, and leads to severe metabolic disorders, including ER stress (21).

5.3 Physical exercise and AMPK contribution to inflammation

As previously stated in the text, obesity and the IR associated are accompanied by a chronic inflammatory process where C-reactive protein and cytokines such as TNFα, IL-1 and IL-6, among others, are pathologically elevated. PE is recognized for its potential effect in regulating inflammation, meaning that in chronic disease conditions it stimulates an anti-inflammatory environment. Much of this effect is due to the endocrine role of skeletal muscle, which, in response to muscle contractions, expresses, synthesizes and releases multiple anti-inflammatory cytokines, such as IL-10 and TGF-β, which have been shown to limit beta cell damage (36). According to Angulo et al. (36) there are studies reporting that both IL-10 and TGF-β activate AMPK. These studies also demonstrate that increased AMPK activity inhibits both LPS and NF-κB signaling, and the consequent activation of proinflammatory cytokines (16,36) (Fig. 6.C). IL-6, although it increases considerably in endurance activities playing multiple roles in metabolic and inflammatory regulation, can have an anti-inflammatory performance. It also could be essential for physiological processes such as the reduction of visceral fat associated with exercise and the proliferation of pancreatic beta cells, preventing their apoptosis, while increasing the secretion of incretins such as GLP-1 and stimulating autophagy, which in turn stimulates insulin secretion (27,36).

5.4 Physical exercise and AMPK contribution to autophagy

Aerobic exercise has been found to decrease ATP levels which activates AMPK, which promotes autophagy in muscle, liver, and adipose tissue alleviating IR. AMPK does this by directly phosphorylating ULK1 or indirectly by inactivating mammalian target of rapamycin complex 1 (mTORC1), causing it to dissociate from ULK1 and activating it (12,14,16,24). PE is able to reduce the level of ROS, which induces autophagy (26), but as mentioned above, it is also capable of inducing ROS with a beneficial effect. Specifically, it induces superoxide ion and hydrogen peroxide, which are the main ROS that, through AMPK coming from this PE, regulate the ULK1 complex and activate autophagy (18). In these cases, AMPK facilitates the autophagy process to eliminate dysfunctional organelles and recycle energy precursors and prevent apoptosis (12,26), in addition to inhibiting the accumulation of hepatic lipids (25). And as mentioned before, autophagy has anti-inflammatory properties and attenuates oxidative damage (24–26). Therefore, AMPK signaling has been proposed as a therapeutic target for the treatment of metabolic diseases with inhibited autophagy, such as obesity and DM2 (12,26) (Fig. 6.D). Other studies have observed that exercise

mitigates IR by stimulating the short-chain FA pathway to activate autophagy (14).

On the other hand, downregulation of AMPK inhibits autophagy (26). Akt-activated mTORC1 in the presence of insulin phosphorylates and inactivates ULK1 and Atg13, resulting in inhibition of autophagy. However, in the presence of FGF21 (an mTOR inhibitor) autophagy is induced (18,24,27). Furthermore, FGF21 also activates NRf2 antioxidant signaling, suppresses the NF-κB pathway, enhances AMPK-activating adiponectin production, increases FA oxidation, and promotes thermogenesis. The apparent contradictory effects of obesity-associated Atg7 downregulation may be better understood if one considers that Atg7-induced inactivation prevents obesity since resistance to FGF21 exists in the obese, but not in the lean state, due to downregulation of its receptor machinery (18,26). In patients with obesity, insufficient autophagy can be improved by upregulation of this process, which in turn improves insulin sensitivity (18).

5.5 Pharmacological activators of AMPK

As mentioned above, along with an active lifestyle and a balanced diet, medicine also contribute to an improvement in insulin sensitivity. Given the therapeutic effects associated with AMPK activation, it is not surprising that many AMPK-activating compounds have been identified. The proportion of the effect of these compounds that can be attributed to AMPK depends not only on the specificity of the drug, but also on the particular mechanism of AMPK activation (37). In practice, AMPK can be activated indirectly by any modulator that causes AMP or calcium accumulation (33). The most commonly used mechanism is that of agents that increase intracellular AMP, thereby indirectly activating AMPK. By inhibiting complex I of the mitochondrial respiratory chain, they inhibit mitochondrial respiration and the consequent production of ATP, in order to decrease the cellular energy state (33,37). Instead, there are mechanisms that activate AMPK directly without any significant change in cellular ATP or AMP levels. These activators induce conformational changes in the AMPK complex, leading to its activation through a direct interaction with the glycogen-binding domain and the kinase domain (33,37).

Metformin. It is a medicine that increases cellular levels of AMP activates AMPK in many tissues, including adipose tissue and skeletal muscle (32). Metformin is an antidiabetic medicine and a large proportion of its glycemic-lowering properties and improvement of peripheral insulin sensitivity are thought to be mediated through activation of AMPK (37). However, the role of AMPK has been called into question by recent work showing that metformin reduces blood glucose levels in animal models of AMPK knockout or LKB1 knockout. Therefore, further studies are required to distinguish the AMPK-dependent and independent effects of metformin (33).

TZDs. Las thiazolidinediones (TZDs), also known as glitazones, are a class of insulin-sensitizing medicine that include troglitazone, pioglitazone, and rosiglitazone. TZDs act primarily by activating peroxisome proliferator-activated nuclear hormone receptors (PPARs), particularly PPARγ. TZDs rapidly activate AMPK and exert their antidiabetic effect in various tissues, including skeletal muscle, liver, and adipose tissue, and the activation mechanisms are associated with AMP accumulation. Furthermore, TZDs treatment induces adiponectin expression and release from adipocytes, which in turn activate AMPK in skeletal muscle and liver, resulting in increased glucose uptake and FA oxidation, and decreased hepatic glucose production. Therefore, AMPK it is activated by TZDs through different mechanisms. (32,33). In DM2 prevention trials, metformin and TZDs independently decreased the progression from impaired glucose tolerance to DM2 by 31% and 70%, respectively, versus a 70% decrease induced by lifestyle changes (diet and exercise). Despite these results in preventing progression to diabetes, TZDs use has recently been reduced due to side effects (32).

AICAR y Component-13. The 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) AMPK activates AMPK directly by functioning as an AMP analogue. It is administered as a prodrug and is taken up by cells from adenosine transporters and phosphorylated by adenosine kinase, thereby metabolizing the AMP analogue (ZMP). Similar to cellular AMP, ZMP binds to AMPK without altering ATP level or oxygen uptake, which occurs with many AMPK activators through inhibition of mitochondrial function. A new AMPK-activating AMP analogue, 5-(5-hydroxy-isoxazol-3-yl)-furan-2-phosphonic acid compound 2 (C2), has recently

been reported and is administered as the prodrug Component 13. C2 is more potent and has a higher specificity for AMPK than AMP or ZMP, but unlike the latter, it only activates AMPK complexes containing AMPKα1. (33,37).

Thienopyridine (A-769662), benzimidazole (Compound 911), Salicylate y MT 63–78. A-769662, like AMP, it causes allosteric activation of AMPK and protects it from dephosphorylation at Thr-172, which is absolutely necessary for AMP-dependent activation of AMPK. However, unlike AMP, A-769662 shows a high specificity for phosphorylation at Ser108. Thus, A-769662 and AMP have different binding sites in the AMPK complex and different activation mechanisms. Recently, another direct AMPK activator, compound 911, has been identified, which is 5-10 times more potent than A-769662 in allosteric activation of AMPK. In the case of salicylate from aspirin, it has a high structural similarity with A-769662, so it also activates AMPK allosterically by binding directly to Ser-108. However, salicylate antagonizes the effect of A-769662. Mice treated with salicylate were shown to have higher rates of FA oxidation and reduced circulating FA levels in an AMPK-dependent manner, in addition to marked anti-inflammatory effects. Recently, another direct AMPK modulator, MT 63–78, has been identified to also allosterically activate AMPK. The effect of MT 68–78 is highly selective for the AMPK complex containing the AMPKβ1 subunit, as observed for A-769662 and salicylate, and without any significant change in cellular ATP and AMP levels (33,37).

6 Conclusions

Physical exercise, specifically the one which combines strength and resistance exercises and is performed long-term at a moderate intensity, has been shown to be able to offer an improvement in metabolic pathologies such as obesity and type 2 diabetes mellitus, and also in associated metabolic dysfunctions such as insulin resistance. AMPK is a mechanism by which an improvement in insulin sensitivity is achieved and is activated by physical activity, and also by medicine. Therefore, together with a healthy lifestyle and diet, and with some medicines, physical exercise could be defined as a powerful therapeutic tool to prevent and treat insulin resistance. Physical exercise achieves this mainly by increasing muscle mass and basal metabolism, which inhibit the mechanisms by which IR is induced. However, further research is required to optimize intervention strategies and better understand the molecular mechanisms involved in this insulin resistance.

Abbreviations

Akt	Protein kinase B
AMPK	AMP-activated protein kinase

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Atg	Autophagy gene
ATP	Adenosine triphosphate
DG	Diglycerol
DM2	Diabetes mellitus type 2
ER	Endoplasmic reticulum
FA	Fatty acids
FFA	Free fatty acids
FGF21	Fibroblast growth factor
GIP	Glucose-dependent insulinotropic polypeptide
GLP1	Glucagon-like peptide
GLUT4	Glucose transporter type 4
GSK3β	Glycogen synthase kinase 3 beta
HbA1c	Glycated hemoglobin
IL-10	Interleukin-10
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IR	Insulin resistance
IRS1	Insulin receptor substrate
JNK	C-Jun amino terminal kinase
LPS	Lipopolysaccharide
mTORC1	Mammalian target of rapamycin complex 1
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PDK	Pyruvate dehydrogenase kinase
PE	Physical exercise
PGC-1α	Transcription cofactor
PI3K	Phosphatidylinositol-3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-triphosphate
PTEN	Phosphatase and tensin homolog
PTP-1B	Phosphor-tyrosine phosphatase 1B
ROS	Reactive oxygen species
Ser/Thr	Serine/threonine
SHIP-2	SH2-containing inositol phosphatase 2
SOCS	Suppressor proteins of cytokine signaling proteins
TGF-β	Transforming growth factor β
TNF-α	Tumor necrosis factor α
Tyr	Tyrosine
ULK1	Unc-51 Like Autophagy Activating Kinase 1
UPR	Unfolding protein response

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