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review article

Effects of physical exercise in molecular parameters of the route of obesity and insulin signaling

Efeitos do exercicio físico em parâmetros moleculares da via de sinalização da insulina e obesidade

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Abstract – The prevalence of obesity and diabetes mellitus has increased significantly in recent years and the knowledge that adipose tissue has endocrine activity and plays important roles in regulating inflammation and energy metabolism by molecular mechanisms among others is a source of new studies. This study is aimed at assessing the molecular mechanisms involved in obesity and diabetes mainly in peripheral tissues as well as the relationship of exercise in this context in the form of a literature review. The methodology used was a bibliographic survey in the main databases SciELO and PubMed of articles published between 1998 and 2012. Studies have demonstrated an interrelation between molecular mechanisms involved in the development of obesity and diabetes in central and peripheral tissues. Several studies have shown that physical exercise greatly contributes to the reduction of prevalence, control and even in the treatment of obesity and diabetes. However, there is need for further studies relating various types of exercise at different intensities and volumes and preferably with humans, as well as the study model, that when using animals, exercise programs should be developed concurrently with fat-rich diets in order to assess physical exercise and its role in the prevention of these diseases.

Key words: Exercise; Insulin resistance; Obesity.

Resumo – *A prevalência da obesidade e diabetes mellitus tem aumentado significativamente nos últimos anos e o conhecimento de que o tecido adiposo tem atividade endócrina e desempenha funções importantes na regulação da inflamação e no metabolismo energético por meio de mecanismos moleculares entre outros é fonte de novas pesquisas. Este trabalho versa sobre os mecanismos moleculares envolvidos na obesidade e diabetes principalmente em tecidos periféricos bem como a relação do exercício físico neste contexto, em forma de revisão bibliográfica. A metodologia foi levantamento bibliográfico nas principais bases de dados: Scielo e PubMed, publicados no período de 1998 a 2012. Os estudos tem demonstrado uma inter-relação entre os mecanismos moleculares envolvidos no desenvolvimento da obesidade e diabetes em tecidos periféricos e centrais. Do ponto de vista do exercício físico, vários estudos demonstram uma contribuição muito grande na diminuição da prevalência, no controle e até mesmo no tratamento da obesidade e diabetes. No entanto há necessidade de estudos mais aprofundados relacionando diversos tipos de exercício físico, em volumes e intensidades diferentes e preferencialmente com humanos, bem como o modelo de estudo, que quando utilizado animais, os programas de exercício devem ser desenvolvidos concomitantemente com alimentação rica em gordura, verificando mais intensamente o exercício físico e o seu real papel na prevenção destas doenças.*

Palavras-chave: *Exercício físico; obesidade; resistência insulina.*

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INTRODUCTION

During the last decades, it has been reported that the adipose tissue is not solely an organ for fat storage, but also an organ with endocrine activity, with important functions, regulating both inflammation and energy metabolism[1]. The metabolic changes associated with changes in adipocyte gene expression by different mechanisms in different organs and tissues are responsible for the redistribution of cellular and molecular signaling both in adipose tissue and in other tissues, suggesting the involvement of transcription factors, inflammatory mediators and formation of free radicals (FR) in the development of obesity.

The prevalence of obesity and type-2 diabetes Mellitu (DM2) have increased significantly in recent years; the relationship of physical exercise in the control and treatment of obesity and insulin sensitivity has been well described in literature[2], but there are still gaps in understanding molecular parameters, where several studies have been conducted in order to understand the molecular mechanisms in peripheral tissues, linking obesity to therapeutic or preventive interventions, given that physical exercise has been considered an important tool to prevent or assist in the treatment of various diseases such as obesity due to increased daily energy expenditure, also contributing to the improvement of cell signaling[3].

The primary aim of this study was to gather studies that describe the mechanisms of weight gain and insulin sensitivity by means of molecular parameters and pro- and anti-inflammatory cytokines in peripheral tissues responsible for the propagation of the signal due to high-fat diet and lack of physical activity as a protective mechanism.

METHODOLOGICAL PROCEDURES

This article is a literature review that included articles published between 1998 and 2012 through the selection of scientific articles searching the following databases: SciELO and PubMed, using keywords such as Diabetes mellitus, diabetes, molecular and biochemical mechanisms and obesity.

Development

Obesity had a different path in its understanding after the discovery that adipose tissue is an organ with endocrine activity capable of producing and releasing substance in the human body, with abnormal adipokine production and activation of some pro-inflammatory signaling pathways related to the disease[4]. Thus, studies have been conducted to identify those that are closely related to obesity and other diseases, and some of them such as tumor necrosis factor α (TNF-a), resistin, adiponectin, IL - 6 (interleukin 6), PAI- 1 (plasminogen activator inhibitor -1), leptin, FFA (Free Fatty Acid), angiotensinogen, visfatin, IL - 1 (interleukin- 1), among others, have been reported. As the adipocyte increases in size or amount, the production and release of these cytokines also increase, and as a result, body weight increases[5].

At cerebral level, specifically in the hypothalamus, the signaling center is stimulated by leptin and insulin and activates both the POMC / CART (*Pro*-opiomelanocortin / Transcription related to amphetamine cocaine) as the NPY / Agrp (Neuropeptide Y / Agouti-related protein), depending specifically on two factors, energy status or deficiency of one of the molecular pathways, which may impair the transduction of hunger or satiety signal[6].

At hypothalamic level, insulin demonstrates increased sensitivity by the action of both leptin and insulin in animals submitted to physical exercise, with the hypothesis that exercise can have appetite suppressive actions by hypothalamic pathway of phosphatidylinositol 3 kinase (PI3K)[7].

There seems to be an inter-relationship between the signaling pathways of leptin and insulin, starting its signaling via Janus Kinase (JAK) and signal transducer and transcription activator (STAT- 3) in the hypothalamus . Leptin and insulin are both able to induce the activation of JAK -2 and STAT -3 phosphorylation. Thus, it is concluded that the hypothalamus, in the JAK-2/STAT-3 pathway, is primarily controlled by leptin, suffering a modulation increased by insulin[8].

Signaling may also occur in the path of the insulin receptor substrate (IRS) and PI3K. Studies have shown that in this case, the effect of insulin predominates on leptin, which causes increased activation of PI3K. As a result, there is a higher rate of neuronal firing and leptin plays an enhancing role[9].

The insulin signaling starts with the intracellular binding to a specific membrane receptor, a heterotetrameric protein with kinase activity composed of two alpha subunits and two beta subunits, called Insulin Receptor (IR)[10]. IR activation results in tyrosine phosphorylation of many substrates, including insulin receptor substrates 1 (IRS -1) and 2 (IRS- 2). The phosphorylation of IRSs proteins creates binding sites for other cytosolic protein called PI3K, promoting its activation.

PI3K plays an important role in the regulation of mitogenesis, cellular differentiation and metabolic effects stimulated by insulin[11]. The phosphorylation of tyrosine sites of SRI proteins to the SH2 domain of the p85 subunit of PI3K activates the associated catalytic site. The enzyme catalyzes the phosphorylation of phosphoinositides at position 3 of the inositol ring to produce phosphatidylinositol-3 phosphate, phosphatidylinositol-3,4-diphosphate and phosphatidylinositol-3,4,5 triphosphate. The activation of PI-3-K increases the serine phosphorylation of the protein kinase B (AKT)[12].

PI3K-related proteins also play an important role in the control of hunger. PI3K activates Akt (Protein Kinase B) and promotes the phosphorylation of FKHR (transcription factor), a protein of the superfamily of Forkhead transcription factors[13]. These proteins can regulate the expression of genes involved in apoptosis, cell cycle, DNA repair, oxidative stress, longevity and growth control[14].

Acute exercise seems to be able to increase phosphorylation of beta-subunit of insulin receptor (IRβ) into tyrosine and increase the phosphorylation of the substrate of insulin receptor 1 (IRS -1) into tyrosine

stimulated by insulin[15]. Exercise also potentiates the effect of insulin in the phosphorylation of insulin receptor substrate 2 (IRS-2) with consequent increase in phosphatidylinositol-3-kinase (PI3K) activity[16]. Furthermore, there is also a greater phosphorylation of Akt into serine, which is an essential protein for the translocation of glucose transporter (GLUT4) to the cytoplasmic membrane[17]. The decrease in body weight by exercise is related to the activation of the mitochondrial metabolism, which has been associated with T2DM.

Physical exercise has been described as a way to control the glucose homeostasis and improve insulin sensitivity in some tissues[3]. The molecular mechanism involved in insulin sensitivity mediated by exercise may be related to increased level or activation of proteins that modulate metabolism[18]. IR, IRS and Akt, are molecules involved in glucose uptake and several studies have shown that physical exercise is sufficient to promote the reversal of insulin resistance in diabetic and obese rats[15,19]. According to O'Gorman[20], a simple acute exercise session can increase insulin sensitivity for up to 16 hours post exercise to modify the GLUT4 content in insulin-dependent tissue, in addition to energy homeostasis and change in insulin sensitivity in tissues such as muscle, liver and hypothalamus in humans.

Study by Pauli et al.[21] assessed the insulin signaling pathway by IR, IRS1 and Akt receptors in adipose tissue, liver and muscle and observed that high-fat diet increased resistance in all tissues by decreasing the phosphorylation of IR, IRS1 and by phosphorylating Akt into serine, decreasing signal transduction.

Related to physical training[21], describes that this had no fully protective effect on insulin resistance in animals exposed to high-fat diet compared to control group; however, when two obese groups were compared, physical training showed significant improvement in phosphorylation of IR, IRS1 and Akt in all tissues: fat, muscle and liver. Similar results were found in other studies using obese animals[19,22], which demonstrated that physical training is effective in improving insulin sensitivity, increasing phosphorylation of IRS - 1/2, and the association of these proteins with PI3K in animals stimulated with insulin compared with control animals.

Hormones such as insulin, once secreted by pancreatic B cell, whose synthesis is primarily activated by increased circulating levels of glucose and also modulated by amino acids and fatty acids, in addition to neural stimuli, act in different tissues, including liver, skeletal muscle and adipose tissue, providing immediate metabolic effects such as increased glucose uptake especially in muscle and adipose tissues, synthesis of proteins, fatty acids and glycogen, as well as blockage of the hepatic glucose production, proteolysis and lipolysis, among others[23].

From the functional point of view, when associated with obesity, insulin stimulates the storage of substrates in adipocyte, which in turn leads to an increased expression and secretion of leptin by this tissue. Acting on the hypothalamus, leptin increases thermogenesis and inhibits appetite[24]. On the other hand, when it acts on the pancreatic islet, reduces insulin secre-

tion, leading insulin and leptin to participate in an endocrine control system whose main objective is to keep energy stocks controlled and regulate the circulating levels of the main substrate of immediately use, glucose[25].

Adiponectin, an anti- inflammatory adipokine, has systemic effect, and its plasma concentration is inversely related to adipose tissue mass and body mass index (BMI). This adipokine increases insulin sensitivity in skeletal muscle and adipose tissue, has anti-inflammatory effects on cells of the immunological system and reduces the formation of atheroma plaque[26]. Therefore, the decrease in plasma adiponectin concentration may be associated with increased inflammation and decreased insulin sensitivity and cardiovascular problems often seen in obese individuals[27].

So far, three adiponectin receptors have been identified: AdipoR1, AdipoR2 and more recently T-cadherin. AdipoR1 and AdipoR2 are receptors with seven transmembrane domains. AdipoR1 shows high expression in skeletal muscle both in humans and in rats. In contrast, AdipoR2 is expressed in the liver of rats and in the liver and skeletal muscle of humans; T-cadherin, although a truncated receptor that lacks of intracellular domain required for signal transduction, may participate in the intracellular signaling cascade, competing with AdipoR1 and AdipoR2[28].

The effects of physical exercise on plasma adiponectin concentration do not indicate significant changes after physical training, perhaps due to the characteristic of subjects, training protocols or exercise intensity[29]. In addition, *in vitro* studies reporting inhibition of the AdipoR expression have demonstrated decrease in glucose uptake, suggesting that the proposed effect of adiponectin on glucose homeostasis in humans can be partly regulated by the levels of the adiponectin receptor expression[30].

Insulin sensitivity can be improved by raising the adiponectin levels, predominantly secreted by differentiated adipocytes and are involved in energy homeostasis, insulin sensitivity, and anti-inflammatory response[31]. However, adipokine is reduced in obese individuals, acting through its receptors AdipoR1 and AdipoR2. AdipoR1 and AdipoR2 interact with the adapter protein containing homology domain with pleckstrin, binding domain with phosphotyrosine and leucine zipper motif, adapter endosomal protein 1 (APPL1), and their interaction plays an important role in the activation of AMPK by adiponectin[32].

It has been shown that the adapter endosomal protein (APPL1) regulates the activity of Akt and exercise shows improvement in insulin signaling in different tissues, which can be attributed in part to the recovery levels of adiponectin receptors and APPL1[21]. Previous studies have shown that physical exercise induce an increase in adiponectin levels and AdipoR1 levels in skeletal muscle suggest that exercise increases insulin action through further increase of APPL1 in the liver of obese rats[33].

Adipokine increases insulin sensitivity and has anti-inflammatory and anti-atherogenic effects and decreased serum adiponectin concentrations have been observed in individuals with insulin resistance, obesity, type-2 diabetes and cardiac diseases[34]. Serum adiponectin concentrations are in-

versely correlated with central adiposity, blood pressure, fasting glucose, insulin resistance and serum insulin concentrations[35]. It has also been shown that adiponectin reduces hepatic glucose production and triacylglycerol concentration in skeletal muscle, thus improving the insulin sensitivity[36].

Both chronic and acute exercises have an effect on glucose consumption and availability, with important implications for individuals with diabetes in terms of chronic metabolic control and acute regulation of glucose homeostasis. The molecular mechanism associated with insulin sensitivity through physical exercise is related to the activation of key proteins in the regulation of glucose metabolism, as APPL1 mediated by Akt, which activated by insulin, results in the modification of GSK3B phosphorylation and increased accumulation of glycogen in the liver of rats[37].

Other cytokines are related to obesity and type-2 diabetes such as elevated TNF- α and IL-6 levels that modulate insulin resistance via several distinct mechanisms, including JNK1, serine phosphorylation into IRS-1, Ikbkinase complex (IKK), NF - KB and activation and induction of suppressor of cytokine signaling 3 (SOCS-3), thus, the activation of the immune response in obesity is mediated by specific signaling pathways, as the enzyme complex with serine kinase activity (JNK and IKK). These events may alter insulin signaling and result in the development of insulin resistance[38].

FINAL COMMENTS

Further studies should be conducted to elucidate the molecular and biochemical mechanisms that physical exercise provides in obese animas. Some issues may be the subject of future investigations on the relationship between molecular and biochemical variables, such as assessing the relationship between two pathways (molecular and biochemical) related to obesity, crossing survey data, checking out which condition comes first in the onset of obesity in animals fed with high-fat diet and the combined action of physical training. Similarly, it would be also important to verify the molecular and biochemical responses of animals exposed to different training models (swimming, weight lifting, running, etc), with different volumes and intensities, thereby determining which activities are most effective in the control and treatment of obesity.

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