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General aspects of muscle glucose uptake

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ABSTRACT

Glucose uptake in peripheral tissues is dependent on the translocation of GLUT4 glucose transporters to the plasma membrane. Studies have shown the existence of two major signaling pathways that lead to the translocation of GLUT4. The first, and widely investigated, is the insulin activated signaling pathway through insulin receptor substrate-1 and phosphatidylinositol 3-kinase. The second is the insulin-independent signaling pathway, which is activated by contractions. Individuals with type 2 diabetes mellitus have reduced insulin-stimulated glucose uptake in skeletal muscle due to the phenomenon of insulin resistance. However, those individuals have normal glucose uptake during exercise. In this context, physical exercise is one of the most important interventions that stimulates glucose uptake by insulin-independent pathways, and the main molecules involved are adenosine monophosphate-activated protein kinase, nitric oxide, bradykinin, AKT, reactive oxygen species and calcium. In this review, our main aims were to highlight the different glucose uptake pathways and to report the effects of physical exercise, diet and drugs on their functioning. Lastly, with the better understanding of these pathways, it would be possible to assess, exactly and molecularly, the importance of physical exercise and diet on glucose homeostasis. Furthermore, it would be possible to assess the action of drugs that might optimize glucose uptake and consequently be an important step in controlling the blood glucose levels in diabetic patients, in addition to being important to clarify some pathways that justify the development of drugs capable of mimicking the contraction pathway.

Key words: diabetes, exercise, glucose uptake, diet, hypoglycemic drugs.

INTRODUCTION

The maintenance of stable levels of glucose is obtained by a complex homeostatic mechanism. During fasting, glucose is maintained via hepatic glycogenolysis or via gluconeogenesis. In a postprandial state, insulin is secreted from pancreatic β-cells and this hormone inhibits hepatic glucose output and promotes the glucose uptake

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into skeletal muscle and adipose tissue. In addition, insulin is important for several cellular processes, such as protein synthesis, gene transcription and metabolism. However, there are further glucose uptake mechanisms that have the purpose of maintaining glucose levels.

Disorders of glucose uptake by peripheral tissues are usually associated to pathological conditions such as obesity, atherosclerosis and type 2 diabetes mellitus (T2D). These conditions are frequently related to the inability of insulin to exert its role in glucose metabolism, especially in tissues with high metabolic activity (such as skeletal muscle), such phenomenon is known as insulin resistance (Razani et al. 2008, Rizza and Butler 1990, Westphal 2008). On the other hand, several studies have described important pathways by which glucose uptake is independent of the proper functioning of the insulin pathway (Lee et al. 1995) or the presence of any morbidity related to insulin resistance (Kennedy et al. 1999). In this context, exercise is one of the main interventions available because muscle contraction stimulates glucose uptake by insulin independent pathways (Lund et al. 1995) and the main molecules involved are adenosine monophosphate-activated protein kinase (AMPK), nitric oxide (NO), bradykinin, AKT, reactive oxygen species (ROS) and calcium. Interestingly, some previous studies showed that patients with T2D have similar composition of skeletal muscle fiber (Vogt et al. 1992, Zierath et al. 1996), expression of GLUT4 protein, and mRNA in response to exercise training (Dela et al. 1995, Hughes et al. 1993) compared with control subjects. With the better understanding about these pathways, it is possible to assess, exactly and molecularly, the importance of physical exercise and diet on glucose homeostasis. In addition, to test the action of drugs that might optimize glucose uptake and consequently be an important step in the control of blood glucose levels in diabetic patients (Musi et al. 2002), as well as to clarify some mechanisms of new drugs, such as PPARδ and AMPK agonists (Narkar et al. 2008), that are commonly called the "exercise pills" and that are being studied in a future perspective for the treatment of T2D. Therefore, in this review, our main aims were to highlight the different glucose uptake pathways and to report the effects of exercise, diet and drugs on their functioning.

GLUCOSE UPTAKE PATHWAYS

Insulin-Dependent Pathway

Through an intracellular cascade reaction, insulin stimulates translocation of glucose transporters (GLUTs) into the cell membrane of the cells responsive to this hormone with subsequent internalization of glucose molecules (Cavalheira et al. 2002, Shepherd and Kahn 1999). In fact, considering all the effects of insulin on glucose metabolism, the regulation of GLUT4 trafficking and consequently glucose uptake is the most important of them (Rowland et al. 2011). In addition, glucose transport is the key step in insulin-regulated glucose metabolism, including glycolysis, glycogen synthesis and lipogenesis, and it is clear that a dysfunction in this process in muscle and adipose tissue represent an important defect in the insulin action (Rothman et al. 1995).

In insulin-responsive tissues such as skeletal muscle, adipose tissue and liver, the action of insulin is initiated by binding to its specific receptor. The insulin receptor is heterotetramer, consisting of two extracellular α subunits (binding fraction) and two transmembrane β subunits (with intrinsic tyrosine kinase), linked by disulfide bonds (Draznin 2006). The activation of the insulin receptor provides a structural change in α subunit leading to autophosphorylation of a tyrosine kinase domain of β subunits (White and Kahn 1994) and subsequent tyrosine phosphorylation of several protein intermediates, including insulin receptor substrate (IRS -1, 2, 3 and 4). Both of these phosphorylated

substrates recognize and bind to domains with homology SH2, especially phosphatidylinositol-3-kinase (PI3-K) (Backer et al. 1992, White and Kahn 1994). This enzyme is a dimer composed of a regulatory subunit (P 85) with two SH2 domains and one SH3 domain associated with a catalytic subunit (P 110). The PI3-K is activated when phosphorylated IRS-1 binds to the SH2 domain, thereby activating its catalytic subunit (Backer et al. 1992, Cavalheira et al. 2002, White and Kahn 1994). The PI3-K promotes the catalysis of the inositol ring of phosphoinositides at position 3 resulting in (3,4,5) phosphatidylinositol triphosphate (PIP3) from (4,5) phosphatidylinositol biphosphate (Cavalheira et al. 2002, van Dam et al. 2005). PIP3 provides the phosphorylation of phosphoinositide-dependent protein kinase 1 (PDK1) which in turn activates protein kinase B (PKB) or AKT (Kohn et al. 1998) and protein kinase C (PKC) (Shepherd and Kahn 1999). Following its recruitment to the cell surface, AKT is activated resulting in the AKT-dependent phosphorylation of many substrates. The connector enhancer of KSR-1 protein (CNK1) was recently implicated in positive regulating insulin signaling through IRS-1 and PI3-K by being part of a complex via that indirectly stimulates the activity of phosphatidylinositol-4-phosphate 5-kinases at the plasma membrane to generate a (4,5) biphosphate-rich microenvironment that is critical for the membrane recruitment of IRS-1 and for the signaling to the PI3-K/AKT cascade (Lim et al. 2010). In adipose and muscle, finally, these kinases stimulate translocation of GLUT4 to the plasma membrane, facilitating the entry of glucose into the intracellular (van Dam et al. 2005) (Figure 1). In addition to glucose uptake, virtually all of insulin's metabolic effects are regulated by AKT. For example, AKT-dependent phosphorylation of glycogen synthase kinase 3 (GSK-3β) leads to the activation of glycogen synthase and enhances glucose storage as glycogen (Rowland et al. 2011, Bouskila et al. 2010). The activation of AKT's kinase activity requires three steps, however, the order of these phosphorylation events is not clear yet (Rowland

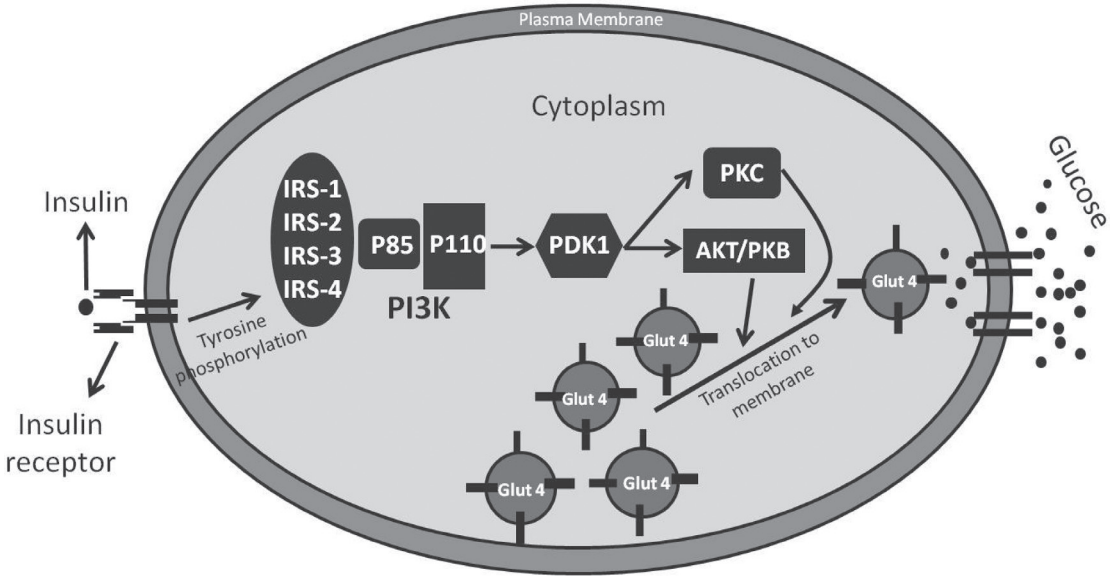

Figure 1 - The insulin activates a number of intracellular signaling proteins that are involved in the insulin-dependent glucose uptake mechanism [e.g., insulin receptor substrate (IRS), phosphatidylinositol-3-kinase (PI3K), regulatory subunit of PI3K (P85), catalytic subunit of PI3K (P110), phosphoinositide-dependent protein kinase 1(PDK1), protein kinase C (PKC), protein kinase B (PKB or AKT), and glucose transporters 4 (GLUT4)].

et al. 2011). The first one is the translocation to the plasma membrane and binding of PIP3. Secondly, the binding of PIP3 induces a conformational change in AKT, which is thought to be a necessary step prior to its phosphorylation at Thr^{308} by PDK-1 and phosphorylation of Thr^{308} by PDK-1 leading to conformational change in the activation loop and exposure of the active site and, consequently, allowing the binding of both adenosine triphosphate (ATP) and the substrate protein (Milburn et al. 2003). Finally, phosphorylation of Ser^{473} probably by the mTORC2 complex also seems to be important. Ser^{473} is a regulatory phosphorylation site which is present in the C-terminal hydrophobic domain of AKT. Various candidate molecules working as kinase that phosphorylates Ser^{473} have been suggested, including protein kinase Cα (PKCα), the integrin-linked kinase, ATM, DNA-PK and autophosphorylation by AKT itself (Dong and Liu 2005). However, the mammalian target of rapamycin (mTOR) in complex with mLST8, mSin and rictor (the mTORC2 complex) has emerged as the strongest candidate for the Ser^{473} kinase (Sarbassov et al. 2005). Phosphorylation of Ser^{473} has been believed to play a dual role in the activation of AKT, acting as an anchorage site for PDK-1 in other AGC family kinases and as an allosteric regulator of AKT activity (Frodin et al. 2002).

Insulin-Independent Pathway

AMP-activated protein kinase (AMPK)

The AMPK protein complex is a family member of protein kinases composed of 12 molecules consisting of subunits α, β and γ (Hardie et al. 2003, Musi and Goodyear 2003). Each α and β subunit has two isoforms (α1 and α2 or β1 and β2), whereas the γ subunit has three isoforms (γ1, γ2 and γ3). The α-subunit has catalytic activity, and β and γ subunits are important in substrate specificity and in maintaining the stability of heterotrimer (Jensen et al. 2008, Jessen and Goodyear 2005). AMPK plays a pivotal role in the glucose uptake, independent of insulin in myocytes. It is stimulated by the contraction of skeletal muscle and is activated by an increase in the AMP:ATP ratio and a decreased in the creatine:phosphocreatine ratio (Chen et al. 2000, Fujii et al. 2000, Winder and Hardie 1996, Wojtaszewski et al. 2003).

The muscle contractile activity alters the cellular energy state resulting in an increase in body metabolic requirement which triggers pathways that consume ATP with consequent increase in the concentration of byproducts, such as AMP (Hardie 2003, Kemp et al. 2003). Increases in levels of AMP activate AMPK allosterically, inducing phosphorylation of threonine residue (Thr^{172}) located in the catalytic α-subunit by LKBI (upstream serine-threonine kinase) (Hardie et al. 2003, Kemp et al. 2003, Musi and Goodyear 2003). Therefore, physiological activation of AMPK occurs during contraction/exercise likely in response to increased binding of AMP and ADP and decreased binding of ATP to the γ-subunit (Richter and Hargreaves 2012).

Recent evidence supports the role of AMPK in cell signaling for the glucose transport by means of 5-aminoimidazole-4carboxamide-1-ß-D-ribonucleoside (AICAR) (Fisher et al. 2005, Ju et al. 2007, Wijesekara et al. 2006). The AICAR mimics the effect of AMP on AMPK. In fact, studies *in vitro* showed that isolated rat muscles, and both healthy and T2D human muscles exposed to AICAR, exhibited an increase on glucose transport in the absence of insulin (Bergeron et al. 1999, Hayashi et al. 1998, Koistinen et al. 2003, Miyamoto et al. 2007). In addition, the combination of AICAR and insulin promoted an additional glucose transport in muscle and neuronal cells (Shah et al. 2011, Fediuc et al. 2006, Hayashi et al. 1998). However, the effect of AICAR on glucose uptake is lost when α2 or γ3 AMPK subunits are deficient (Barnes et al. 2004, Jorgensen et al. 2004, Mu et al. 2001).

The pathways of glucose uptake induced by both muscle contraction and AICAR appear to be distinct. Jorgensen et al. 2004, studying soleus and EDL muscles of mice, showed that muscles of α1 or α2-AMPK knockout (KO) mice when stimulated by muscle contraction, present glucose uptake similar to wild-type mice. However, when stimulated by AICAR, only muscles of α1-AMPK KO mice showed glucose uptake levels preserved. Thus, it can be suggested that AICAR-stimulated glucose uptake is dependent of α2-AMPK subunit. Corroborating with these data, Fujii et al. 2005, studying transgenic mice carrying cDNAs of inactivity α2-catalytic subunits of AMPK, showed that AICAR-stimulated glucose transport was fully inhibited. However, the lack of AMPK α2-activity had no effect on contraction-induced glucose transport.

Lastly, AMPK proves to be an important exercise/contraction-stimulated glucose uptake pathway, mainly, by increased AMP and ADP levels.

Calcium

The repeated contraction of skeletal muscle can provide an increase in myocyte calcium concentrations (Chin 2005, Jessen and Goodyear 2005). This increase has been implicated in GLUT4 translocation and glucose transport (Jessen and Goodyear 2005, Kurth-Kraczek et al. 1999). In addition, calcium stimulates glucose transport in skeletal muscle by pathways, independent of contraction (Youn et al. 1991). The supposed mechanisms by which calcium can stimulate glucose uptake are not fully understood. Potential candidates include calmodulin-protein kinase and protein kinase C (PKC) (Chin 2005, Richter et al. 2001, 2004, Wheatley et al. 2004). The interaction of calcium-calmodulin kinase (CaMK) proved to be an additional mechanism for the activation of AMPK via Thr^{172} phosphorylation, as well as for promoting other possible effects to initiate the GLUT4 translocation (Jensen et al. 2007b, Ojuka 2004, Ojuka et al. 2002, Wijesekara et al. 2006, Wright et al. 2004, 2005).

Evidence showed that caffeine stimulates an increase in intracellular calcium levels in isolated rat muscles with consequent increase in glucose uptake independent of muscle contraction (Terada et al. 2003). In addition, several studies showed that incubation with caffeine increase nucleotide turnover and AMPK activation in muscle from mice and rats independently of muscle contraction (Egawa et al. , Jensen et al. 2007a, Richter and Hargreaves) probably due to the relevant energy demand posed by sarcoplasmatic reticulum Ca^{2+}-ATPase-dependent Ca^{2+} (SERCA) reuptake (Norris et al. 2012, Richter and Hargreaves). Thus, these studies suggested that the increase in glucose uptake is due to metabolic stress triggered by SERCA activation and muscle contraction and not by direct action of calcium.

Nitric oxide (NO)

NO is an endogenous signaling molecule, involved in the regulation of several physiological functions as well as in mediation of a variety of pathophysiological processes (Moncada and Higgs 1993). In addition to its physiological implications in the cardiovascular system (vasodilatation, for example), it has recently been postulated that NO has an important role in glucose uptake by skeletal muscle (Merry et al. 2010a). Studies with animals and humans supported the hypothesis that the glucose uptake pathway stimulated by NO may be independent of both insulin and muscle contraction (Higaki et al. 2001, Henstridge et al. 2009). However, other evidence have shown the importance of proper functioning of this system to optimize the insulin-dependent uptake of glucose (Roy et al. 1998). In humans, inhibition of NO by L-NMMMA decreased glucose uptake in type 2 diabetics and healthy patients without affecting total blood flow (Bradley et al. 1999). Despite the contributions previously reported, some assays have shown that NO plays a role in glucose metabolism independently of insulin pathway. Even after the pharmacological inhibition of PI3K, glucose uptake

stimulated by NO is still preserved (Tanaka et al. 2003). Regarding the participation of NO in glucose uptake stimulated by muscle contraction, studies are inconclusive, although some evidence has indicated that inhibition of NO blocks glucose uptake stimulated by muscle contraction (Roberts et al. 1997). However, other studies using simultaneously either muscle contraction or exogenous mechanisms that stimulate AMPK and an inhibitor of NO, have shown that glucose transport remains normal (Etgen et al. 1997, Higaki et al. 2001). These data suggest that the mechanisms involved in glucose uptake mediated by NO signaling pathways may be distinct from both insulin and muscle contraction pathways. Another interesting finding is the influence of muscle fiber type in glucose uptake mediated by NO. A study with animals demonstrated that inhibition of NO reduces contraction-induced glucose uptake, only in fast twitch muscles (Merry et al. 2010b).

Bradykinin

Bradykinin is a nonapeptide hormone that mediates important physiological effects such as inflammation, vascular permeability, hypotension, edema, smooth muscle contraction and glucose metabolism (Kishi et al. 1998), and most of these actions is mediated by the B2R receptor (Dumke et al. 2002). Studies have shown that bradykinin influences glucose metabolism through both insulin-dependent and insulin-independent pathways (Motoshima et al. 2000). It has been shown that the administration of bradykinin increases glucose uptake in cultured adipocytes and skeletal muscles of the forearm in humans (Duka et al. 2001). In addition, bradykinin reduces hyperinsulinemia, decreases the concentration of plasma free fatty acids, improves glucose tolerance, increases insulin action in target tissues (Henriksen et al. 1998) and enhances glucose transport through exercise (insulin-independent pathway) (Kishi et al. 1998). Furthermore, a relationship between bradykinin and other mechanisms of glucose uptake has been proposed as evidenced for the increased glucose uptake after intra-hypothalamic infusion of leptin (Shiuchi et al. 2001).

Some mechanisms have been proposed to explain how bradykinin interferes in the glucose metabolism. Studies have reported that bradykinin enhances the tyrosine phosphorylation of IRS-1 and thus improves the binding affinity of IRS-1 with the P85 regulatory subunit of PI3K, which increases the translocation of GLUT4 to the plasma membrane. Therefore, the insulin-dependent glucose uptake is improved (Motoshima et al. 2000). Additionally, it has been postulated that the use of angiotensin-converting enzyme (ACE) inhibitors reduces insulin resistance and diabetes risk (Al-Mallah et al. 2010). Some studies have also observed that the ACE inhibitors lead to an increase in glucose uptake in murine skeletal muscle due to increased bioavailability of bradykinin caused by this drug (Shiuchi et al. 2002). However, some mechanisms are still unclear and further investigations are needed in this field.

Reactive Oxygen Species (ROS)

ROS are reactive molecules that have an unpaired electron in their outer layer. Chronic high levels of ROS are associated with the pathophysiology of numerous diseases including diabetes and cardiovascular disease (Powers and Jackson 2008). However, current studies have suggested that physiological levels of ROS, especially of hydrogen peroxide (H_2O_2), may act as signaling molecules in the regulation of gene expression and cellular metabolism (Jackson 2008, Ji 2008, Katz 2007). In skeletal muscle, the production of ROS may be promoted by various stimuli, including hypoxia, insulin and muscle contraction (Merry and McConell).

Relevant evidences demonstrated the ability of exogenous H_2O_2 to stimulate basal glucose uptake in isolated skeletal muscle (Cartee and Holloszy 1990). Corroborating with previous findings, Sandstrom

et al. (Sandstrom et al. 2006) demonstrated that treatment with the N-acetylcysteine (NAC) and ebselen antioxidants reduced the elevation in ROS by contraction and attenuated glucose uptake. In the meantime, studies on human have shown that infusion of NAC did not decrease exercise-stimulated glucose uptake (Merry et al. 2010b).

There is evidence that ROS produced during contraction of skeletal muscle play a role in the regulation of glucose uptake (Merry and McConell 2012). However, the molecular mechanisms by which ROS may regulate glucose uptake in skeletal muscle are still unclear. Sandstrom *et al* (Sandstrom et al. 2006) demonstrated that the antioxidant NAC attenuated AMPK activity and reduced contraction-stimulated glucose uptake in skeletal muscle. However, Merry et al. 2010c investigated glucose uptake in skeletal muscle from AMPK kinase knockout and wild-type mice and showed that the NAC antioxidant similarly inhibited contraction-stimulated glucose uptake. Thus, they suggested that ROS could regulate glucose uptake in skeletal muscle by AMPK independent pathway. In addition, some studies have shown a possible interaction of ROS in the calcium (Merry et al. 2012) and NO (Erickson and Anderson 2008) signaling pathways. However, due to controversial results presented so far, it becomes necessary to conduct new studies.

Convergent mechanisms of glucose uptake: role of AS160 and TBC1D1

It is generally believed that insulin stimulates GLUT4 translocation by molecular mechanisms distinct from contraction pathway (Goodyear et al. 1990, Lee et al. 1995, Lund et al. 1995). However, these two pathways at least partially converge in distal parts. Therefore, there are some signaling molecules related to GLUT4 translocation that are activated by both insulin and muscle contraction, and possibly the most important are the Akt substrate of 160 kDa (AS160) and TBC1D1. AS160 is a Rab GTPase-activating protein (GAP) that modulates GLUT4 trafficking in insulin-sensitive 3T3-L1 adipocytes and L6 myoblasts (Kramer et al. 2006). Under basal conditions, AS160 exists primarily in an unphosphorylated state and retains GLUT4 vesicles intracellular. When cells are treated with insulin, AS160 is rapidly phosphorylated at multiple Akt phospho-motifs (Kane et al. 2002). When 3T3-L1 adipocytes and L6 GLUT4-myc myoblasts were transfected with a constitutively active mutant AS160 (incapable of being phosphorylated at these regulatory sites), a significantly reduced insulin-induced GLUT4 translocation was observed (Sano et al. 2003, Thong et al. 2005). In addition, previous studies have reported increased AS160 phosphorylation with *in vitro* contractions in rat epitrochlearis muscles (Bruss et al. 2005). This suggests that AS160 operates as a common, downstream point of convergence between insulin-mediated and muscle contraction pathways Kramer et al. 2006, using AMPK α2-inactive transgenic mice, observed that AICAR-stimulated AS160 phosphorylation was fully inhibited, whereas contraction-stimulated AS160 phosphorylation was partially reduced in the mice and the combined AMPK α2 and Akt inhibition by wortmannin treatment of AMPK α 2 transgenic mice, did not fully ablate contraction-stimulated AS160 phosphorylation. However, insulin, together with either AICAR or contraction, increased AS160 phosphorylation in an additive manner, indicating that AS160 is a point of convergence linking insulin, contraction, and AICAR signaling. On the other hand, Taylor et al. observed a dissociation between AS160 protein expression and apparent AS160 PAS phosphorylation among types of muscles and identified the AS160 paralog protein TBC1D1 (Taylor et al. 2008). They also observed an increased TBC1D1 phosphorylation *in vivo* stimulated by insulin, contraction, and the AMP-activated protein kinase (AMPK) activator AICAR. Other studies confirmed the role of

TBC1D1 in regulation of glucose metabolism in skeletal muscle in response to contraction and insulin stimuli (An et al. 2010, Pehmoller et al. 2009, Szekeres et al. 2012).

ROLE OF PHYSICAL EXERCISE, DIET, AND PHARMACOLOGICAL AGENTS ON THE GLUCOSE UPTAKE PATHWAYS

Physical Exercise and Glucose Uptake

Several studies have reported benefits of physical training and muscle contraction in the treatment and prevention of T2D, due to optimization of glucose uptake by insulin-dependent and independent pathways (Hayashi et al. 1997, Heinonen et al. 2012). Regarding the effects of exercise on insulin dependent pathway, it proved to be effective in improving insulin action in skeletal muscle of insulin-resistant and diabetic patients (Eriksson 1999). However, it is noteworthy that physical training contributes differently to glucose uptake in different tissues such as skeletal muscle and adipose tissue (Reichkendler et al. 2013). Many of the beneficial actions of exercise on glucose transport mediated by insulin is due to the increased GLUT-4 protein expression (Goodyear et al. 1992) and a better adaptation of enzymes involved in glucose phosphorylation and oxidation (Holloszy and Hansen 1996, Ivy et al. 1999).

Considering the important role of proteins of the insulin-dependent glucose uptake pathway, numerous studies have been conducted to clarify the role of exercise on the activity and expression of these proteins. In rodents, King et al. 1993 demonstrated that the exercise-induced translocation of the GLUT-4 in obese Zucker rats were similar to lean animals. Other studies have shown that physical training leads to the phosphorylation of insulin receptor tyrosine and enhance IRS-1 protein expression (Hevener et al. 2000). However, there was no change in protein expression of insulin receptor β-subunit, p85 subunit of PI3-K and AKT/PKB (Hevener et al. 2000). It is noteworthy that physical training decreasing inflammatory markers as tumor necrosis factor α (Sheibani et al. 2012, Kirwan and del Aguila 2003), C-reactive protein (Jorge et al. 2011, Kadoglou et al. 2007) and interleukin-18 (Kadoglou et al. 2007) in skeletal muscle and body fat mass (Sheibani et al. 2012, Kadoglou et al. 2007). This effect is important to increase expression of GLUT-4 (Kirwan and del Aguila 2003), IRS-1 (Jorge et al. 2011) and insulin sensitivity (Kirwan and del Aguila 2003). Beyond the direct benefits in the insulin-dependent glucose uptake pathway, physical training increases maximal aerobic capacity (Cortez et al. 1991), and raises the levels of enzymes involved in glucose catabolism (hexokinase and citrate synthase) (Banks et al. 1992, Brozinick et al. 1993, Cortez et al. 1991).

Cusi et al. (2000), studying patients with T2D, demonstrated that 24 hours after a single exercise session (Cycle Ergometer 1h of exercise at 65% of VO2max) there was an increase in tyrosine phosphorylation of the insulin receptor and IRS-1 in skeletal muscle. However, the activity of PI3-K associated with IRS-1 was not elevated after exercise. Additionally, Jorge et al. 2011, studying the role of resistance, aerobic and combined training in glycemic control of patients with T2D, showed that both types of training were effective in improving glycemic control. Furthermore, resistance training increased at 90% the IRS-1 expression. Some studies have demonstrated the role of chronic hypoxia on glucose metabolism (Gamboa et al.). Mackenzie et al. 2012, also studying patients with T2D, showed that intermittent exercise during moderate hypoxia presented better results in insulin resistance index and glucose disposal when compared with the same intensity exercise performed in normoxia.

Therefore, as shown in above studies, exercise can provide direct and indirect benefits for insulin resistant and diabetic patients. However, further studies are needed to clarify and reveal new therapeutic mechanisms associated with physical exercise.

Regarding the effects of exercise on insulin independent pathway, exercise plays an important role in insulin-independent glucose uptake (Santos et al. 2008). During exercise there is an over-activation of the sympathetic nervous system, resulting in increased catecholamines levels, which are responsible for inhibiting the secretion of insulin and stimulating the secretion of glucagon from the pancreas. Furthermore, there is an increase in cortisol levels which are known to enhance insulin resistance (McMurray and Hackney 2005).

Most studies that investigated the insulin-independent glucose uptake mechanisms were performed *in vitro* and used the muscle contraction to induce activation of several pathways (Santos et al. 2008). However, there is consensus that the most simple and effective way to stimulate systemic muscle contraction is through physical exercise. Therefore, all the benefits demonstrated by muscle contraction in insulin-independent glucose uptake can be extrapolated to an exercise session.

As shown previously, many biological pathways have played an important role in insulin-independent glucose uptake mechanisms (Santos et al. 2008). The main pathways investigated regarding the impact of muscle contraction/exercise on insulin-independent glucose uptake are: AMPK, NO, ROS, AKT, calcium, bradykinin (Figure 2).

Diet and Glucose Uptake

AMPK is activated by metabolic stresses that either inhibit ATP production (e.g. hypoglycaemia) or accelerate ATP consumption (e.g. muscle contraction). Once activated, it switches on catabolic pathways that generate ATP, while switching off biosynthetic pathways and other processes that

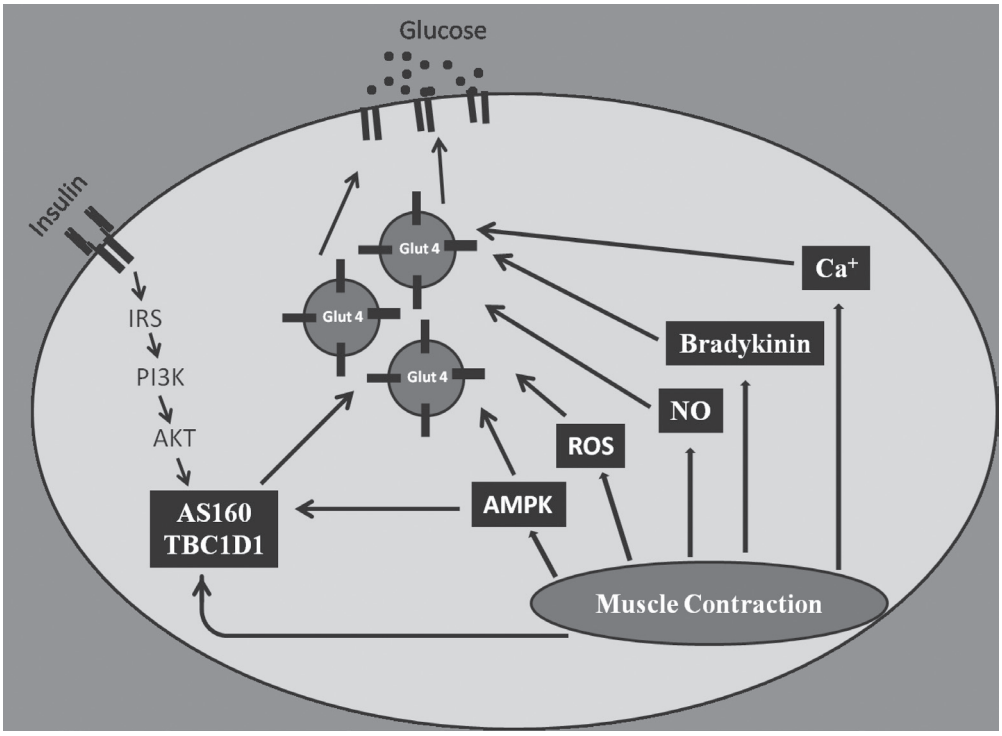

Figure 2 - Muscle contractions cause translocation of the glucose transporter proteins (GLUT4) to the cell membrane. Contraction activates a number of signaling proteins that might be involved in the exercise signaling mechanism [e.g., AMP-activated protein kinase (AMPK), calcium, nitric oxide (NO), bradykinin, Akt substrate of 160 kDa (AS160), TBC1D1 and reactive oxygen species (ROS)].

consume ATP. Its key roles in maintaining energy balance suggest that it would also be an important player in the derangements of energy metabolism that occur in conditions like obesity, metabolic syndrome and T2D (Hardie and Sakamoto 2006). Developed and developing countries underwent or are undergoing fast nutrition transition from a healthy traditional high-fiber, low-fat, low-calorie diet, toward increasing consumption of calorie-dense foods containing refined carbohydrates, fats, red meats, and low fiber. In addition, a decreased levels of exercise in the general population lead to increases in obesity, the metabolic syndrome and T2D. The metabolic syndrome involves a set of risk factors for cardiovascular disease such as insulin resistance, hypertension, altered plasma lipids (mainly hypertriglyceridemia and low high-density lipoprotein cholesterol), and abdominal obesity (Hardie 2008, Misra et al. 2010). Risk of developing T2D is greatly increased by metabolic syndrome, which appears to orchestrate the adaptive physiology of energy deficit, suggesting that the sedentary modern human could be suffering from chronic suboptimal AMPK activation (Mor and Unnikrishnan 2011).

Regarding the glucose uptake insulin-dependent pathway, the nutrient availability, growth factors as well as energy metabolism and stress, all regulate mTOR activity, which plays an important role both in insulin signaling and in the regulation of cellular function in response to nutritional modifications (Matsakas and Patel 2009, Rennie 2007). On the other hand, glucose deprivation is able to lead activation of AMPK in cultured mammalian cells (Salt et al. 1998); however, regulation of AMPK by glucose in vivo may be normally restricted to specialized cells, including pancreatic β-cells and hypothalamus cells, of which the latter is the inhibitor of feeding behavior in response to hypoglycemia (Kang et al. 2006). In this scenario, the rate of glucose metabolism responds to physiological fluctuations in blood glucose and there is evidence that AMPK activity correlates inversely with glucose over a physiologically relevant concentration range (Hardie and Sakamoto 2006, Minokoshi et al. 2004).

Lastly, AMPK activation has potential to lower plasma glucose by repressing expression of enzymes of gluconeogenesis in the liver and by increasing glucose uptake by muscle and other tissues. Also, to reduce hypertriglyceridemia, as well as elevated storage of triglycerides in muscle and liver by inhibiting fatty acid and triglyceride synthesis and stimulating fatty acid oxidation and mitochondrial biogenesis (Hardie 2008). In this field, Musi et al reported that novel AMPK-specific compounds are allowing researchers to examine whether this enzyme is a useful pharmacologic target for the treatment of human disease and whether chronic activation of AMPK will be safe (Sriwijitkamol and Musi 2008, Li et al. 2012).

Hypoglycemic Drugs and Glucose Uptake

T2D is a prevalent metabolic disorder characterized by elevated blood glucose levels (hyperglycemia). Currently, there are several pharmacological interventions available for treating this condition. With regards to type 1 diabetes mellitus, the main intervention is the subcutaneous administration of insulin (Krentz and Bailey 2005). On the other hand, the use of insulin in T2D is only necessary in some cases (Guillausseau et al. 2008), and the treatments frequently used are oral hypoglycemic drugs, which are drugs that act either on pancreatic β-cells increasing insulin secretion (sulphonylureas or metaglinides) or medications for the improvement of peripheral sensitivity to insulin (biguanides and thiazolidinediones). In addition to these classes of drugs, there are also agents that inhibit intestinal α-glucosidase (Krentz and Bailey 2005), which are able to reduce postprandial hyperglycemia and they modulate the intestinal system of incretins, either by increasing endogenous glucagon-like peptide-1

(GLP-1, dipeptidyl peptidase-4 inhibitors) or by mimicking the action of GLP-1 (GLP-1 agonists) (Drucker et al. 2011). Here, we emphasize the biguanides (metformin) and PPARγ agonists (thiazolidinediones or glitazones).

Metformin is considered the main oral hypoglycemic agent used in the treatment of T2D due to its characteristics of action, efficacy and safety (Bennett et al. 2012). The main effect of this drug is to acutely decrease hepatic glucose production, mostly through a mild and transient inhibition of the mitochondrial respiratory chain complex I (Krentz and Bailey 2005, Viollet et al. 2012). The molecular mechanisms of action of metformin are not fully understood, but some studies have demonstrated a close relationship between the metformin and the activity of some enzymes involved in carbohydrate metabolism, such as AMPK (Musi et al. 2002). The resulting decrease in hepatic energy status activates AMPK, a cellular metabolic sensor, providing a generally accepted mechanism for the action of metformin on hepatic gluconeogenesis. Respiratory chain complex I, but not AMPK, is the primary target of metformin. This was strengthened by showing that the metabolic effect of the drug is preserved in liver-specific AMPK-deficient mice (Viollet et al. 2012). It is worth remembering that AMPK inhibits gluconeogenesis and glycogenolysis, stimulates glycogenesis in hepatocytes, and increases glucose uptake in peripheral tissues (Zang et al. 2004, Zhou et al. 2001). Besides the effects on the liver and skeletal muscle, studies have shown that metformin activates AMPK in aortic endothelial tissue *in vivo* (Zou et al. 2004). Therefore, it can be stated that some of the mechanisms of action of metformin may be explained by AMPK activation (Schultze et al. 2012, Viollet et al. 2012).

Metformin is also able to reduce the progression of states of pre-diabetes, as it was observed in the Diabetes Prevention Program trial (Knowler et al. 2002). Beyond its effect on glucose metabolism, metformin has been reported to restore ovarian function in PCOS (polycystic ovary syndrome), to reduce fatty liver, and to lower microvascular and macrovascular complications associated with T2D. Its use has also been suggested as an adjuvant treatment for cancer or gestational diabetes (Aldea et al. 2011, Belda-Iniesta et al. 2011).

Treatment with the first clinically approved thiazolidinediones (TZDs), troglitazone, was withdrawn from the market because of cases of severe liver toxicity, but rosiglitazone and pioglitazone entered the market in the 1990s. In 2010, the United States FDA (Food and Drug Administration) and other agencies restricted the use of both rosiglitazone and pioglitazone, and the European Medicines Agency even recommended suspension of the marketing authorization for rosiglitazone giving its cardiovascular risk profile (Phielix et al. 2011). The mechanism of action of TZDs involves the binding to nuclear receptors PPARγ (peroxisome-proliferator-activated receptors type gamma). After binding, there is a conformational change in the receptor, which allows the connection with the retinoic acid receptor (RXR) and recruitment of one or more co-activators. The interaction of this complex heterodimer with the nuclear regions determines responsive transcription of approximately 500 genes, some of which are closely related to lipid metabolism, glucose and cell differentiation (Owen et al. 2000). Corroborating with these possible mechanisms, studies have shown an improvement in insulin sensitivity in muscle, liver and adipose tissue when individuals are treated with glitazones for 3 months (Abrahamson 2003), which demonstrates the therapeutic potential of these drugs in the treatment of T2D. The TZDs act mainly by improving peripheral uptake and utilization of glucose in muscle and adipose tissue. However, the mechanisms by which glitazones increase the uptake of glucose are not fully understood. *In vitro* studies showed that cultured cells in the presence

of troglitazone become insulin responsive, with an absolute rate of insulin-stimulated glucose uptake increase under these conditions (troglitazone) (Hamm et al. 1999). *In vivo* study that used euglycemic hyperinsulinemic clamp combined with an oral glucose load before and after 3-month treatment with pioglitazone or placebo, reported that pioglitazone is effective for ameliorating insulin resistance in T2D subjects by enhancing splanchnic glucose uptake as well as peripheral glucose uptake (Kawamori et al. 1998). These data were corroborated by a systematic review (Natali and Ferrannini 2006). In addition, thiazolidinediones could improve synergic action of insulin and exercise. Hällsten *et al* found that rosiglitazone (but not metformin) improved insulin responsiveness in resting skeletal muscle and doubled the insulin-stimulated glucose uptake rate during physical exercise in patients with newly diagnosed T2D (Hallsten et al. 2002). A common mechanism that may explain much of the influence of TZDs on glucose uptake could be through the AMPK pathway. AMPK has been implicated in the insulin-sensitizing actions of TZDs: a study has revealed the influence of intravenous infusion of the AMPK activator 5-aminoimidazole 4-carboxamide riboside (AICAR) under euglycemic and iso-insulinemic conditions in insulin-resistant high-fat-fed rats. The authors found that rosiglitazone treatment significantly enhanced AICAR-stimulated whole-body glucose disposal by 27% and a 44% greater glucose infusion rate was required to maintain euglycemia (Ye et al. 2006). Both AICAR-stimulated glucose uptake and glucose incorporation into glycogen in muscle and adipose tissue were enhanced. Finally, the enhanced glucose uptake and glycogen synthesis in muscle were associated with increased activity of total AMPK and the AMPKalpha2 subunit (Ye et al. 2006). In this context, therapy with glitazones have beneficial effects on glycemic control; however, some of the adverse effects such as weight gain, edema, heart failure, anemia, hepatotoxicity, and others (Nissen and Wolski 2007) may limit the use of TZDs.

CONCLUSION

With a better understanding about these pathways, it is possible to evaluate, exactly and molecularly, the importance of physical exercise and diet on glucose homeostasis. Furthermore, to test the action of drugs that might optimize glucose uptake and consequently be an important step in controlling blood glucose levels in diabetic patients. There is no potential conflict of interest.

RESUMO

A captação de glicose nos tecidos periféricos é dependente da translocação dos transportadores de glicose GLUT4 para a membrana plasmática. Estudos mostram a existência de duas principais vias de sinalização que induzem à translocação do GLUT4. A primeira e amplamente investigada é a via de sinalização ativada pela insulina por meio do substrato 1 do receptor de insulina e fosfatidilinositol-3-quinase. A segunda é a via de sinalização independente da insulina que é ativada, principalmente, pela contração muscular. Indivíduos com diabetes mellitus tipo 2 apresentam uma redução na captação de glicose estimulada pela insulina devido à resistência insulínica. Contudo, esses indivíduos geralmente apresentam captação de glicose normal durante o exercício. Neste contexto, o exercício físico é, reconhecidamente, uma das intervenções mais importantes na estimulação da captação de glicose por vias insulino-independentes, cujas principais moléculas envolvidas são: proteína quinase ativada por adenosina monofosfato, óxido nítrico, bradicinina, AKT, espécies reativas de oxigênio e cálcio. Nesta revisão, os objetivos são: destacar as particularidades das diferentes vias de captação de glicose e relatar os efeitos do exercício físico, da dieta e de medicamentos sobre o funcionamento das mesmas. Também, entender molecularmente a importância do exercício físico e da dieta na homeostase glicêmica e, avaliar à ação de fármacos que melhoram a captação de glicose, o que é um importante ponto na eficácia

do controle glicêmico de pacientes diabéticos, bem como esclarecer alguns mecanismos que justificam o desenvolvimento de novos fármacos com fins de mimetizar a via contração muscular.

Palavras-chave: diabetes, exercício físico, absorção de glicose, dieta, fármacos hipoglicemiantes.

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