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Exercise Causes Muscle GLUT4 Translocation in an Insulin-Independent Manner

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Abstract

Glucose uptake in skeletal muscle is dependent on the translocation of GLUT4 glucose transporters to the plasma membrane. The most important stimulators of glucose transport in skeletal muscle are insulin and exercise. Glucose uptake in skeletal muscle during exercise induces acceleration of many processes compared to the resting state. The scientific literature does not underline the role played by muscle contraction to increase glucose uptake with insulin-independent mechanisms. Search on Pub Med (May 05, 2015) using the key words "contraction and glucose uptake and muscle" gives 717 reports, while a search using the key words "insulin and glucose uptake and muscle" cites 5676 publications. The present paper describes the role of exercise in the muscle glucose uptake. Contraction of muscle induces GLUT4 translocation in the absence of insulin. There are different intracellular "pools" of GLUT4, one stimulated by insulin and another one stimulated by exercise. The roles exerted by AMPK, AICAR, calcium, NO, glycogen and hypoxia in the glucose uptake during exercise are emphasized. The effects of these phenomena on human wellness are reported.

Keywords: Glucose; GLUT4; Muscle; Exercise

Introduction

The population statistics of most countries of the world are indicating that industrialization and computerization have been associated with an increase in sedentary behavior and more recently with a significant shift from healthy weight to overweight. In general, this change in the overweight/obesity prevalence is attributed by health professionals to suboptimal diet and physical activity practices.

The beneficial effects of physical exercise on the decreased insulin sensitivity caused by detrimental lifestyle have been demonstrated by experimental evidences. In epidemiological studies, disease prevention has been considered at three levels: primary (avoiding the occurrence of disease), secondary (early detection and reversal), and tertiary (prevention or delay of complications) [1-5]. The major purpose of physical exercise for primary prevention and treatment of lifestyle-related diseases is to improve insulin sensitivity [6-9]. It is known that, during physical exercise, glucose uptake by the working muscles rises 7 to 20 times over the basal level, depending on the intensity of the work performed[10]. However, intense exercise provokes the release of insulin-counter regulatory hormones such as glucagon and catecholamines, which ultimately counter-balance insulin action[11-16]. Continued physical training improves the reduced peripheral tissue sensitivity to insulin in impaired glucose tolerance and Type II diabetes, along with regularization of abnormal lipid metabolism. Furthermore, combination of salt intake restriction and physical training ameliorates hypertension. In practical terms, before diabetic patients undertake any program of physical exercise, various medical examinations are needed to determine whether they have good glycemic control and are without progressive complications. Because the effect of exercise that is manifested in improved insulin sensitivity decreases within 3 days after exercise and is no longer apparent after 1 week, a continued program is needed.

Muscle glucose uptake [17] can be separated into three sequential steps, i.e. delivery of glucose from the blood to the muscle, transport across the sarcolemma by a GLUT, and irreversible phosphorylation to glucose-6-phosphate by an HK isozyme. Each of these steps can serve as a barrier to MGU and, thus, are important in regulating glucose influx. During resting conditions, the transport step exerts the most control in regulating MGU, as GLUT1 (1–4) or GLUT4 [18,19] overexpression augments basal MGU. Previous work suggests that normal GLUT4 content is sufficient for increases in MGU during exercise, because GLUT4 overexpression alone does not further increase exercise-stimulated MGU [20]. Instead of glucose transport, glucose phosphorylation is a primary limitation of exercise-stimulated MGU [21,22]. Heterozygous GLUT4 knock-out mice serve as a useful tool for examining the impact of reductions in glucose transport capacity on MGU[23-26].

Insulin stimulation and physical exercise are the most physiologically relevant stimulators of glucose transport in skeletal muscle [27,28] and interestingly in patients with Type 2 diabetes,

insulin- but not contraction-stimulated glucose transport is impaired [29].

Both insulin and exercise/muscle contraction increase skeletal muscle glucose uptake by translocation of glucose transporters from an intracellular location to the plasma membrane and t-tubules. GLUT4 is the predominant glucose transporter isoform expressed in skeletal muscle. Early studies have demonstrated that there are distinct proximal signaling mechanisms responsible for the stimulation of GLUT4 translocation and glucose transport by insulin and exercise. Insulin signaling involves the rapid phosphorylation of the insulin receptor, insulin receptor substrate-1/2 (IRS-1/2) on tyrosine residues, and the activation of phosphatidylinositol 3-kinase (PI3-K)[30,31]. In contrast, exercise and muscle contraction have no effect on insulin receptor and IRS-1 phosphorylation or on PI3-K activity[32], and muscle-specific knockout of the insulin receptor does not impair contraction-stimulated glucose transport [33,34]. Clearly, these data demonstrate that the initiating signals that lead to GLUT4 translocation by insulin and exercise in skeletal muscle are distinct.

Stimulation of insulin secretion by glucose involves the enhanced synthesis of ATP by mitochondria [35] and closure of ATP-sensitive K + channels [36]. Subsequent depolarization of the plasma membrane [37] then opens voltage-sensitive (L-type) Ca2+ channels [38] causing insulin containing vesicles to fuse at the plasma membrane[39]. The mechanisms that link changes in glucose concentration to the regulation of B-cell genes are less well understood[40,41]. Recently, we have demonstrated that AMP-activated protein kinase (AMPK) is involved in the regulation of gene expression by glucose in this cell type[42]. AMPK is a multisubstrate, heterotrimeric serine/threonine protein kinase, consisting of a catalytic α-subunit and non-catalytic β- and γ-subunits [43].

Regular physical activity leads to a number of adaptations in skeletal muscle that allow the muscle to more efficiently utilize substrates for ATP production and thus become more resistant to fatigue. The three major adaptations to exercise training are: 1) muscle fiber type transformations as defined by the expression of specific contractile proteins (myosin heavy chain isoforms), 2) increases in mitochondrial activity and content, and 3) increases in GLUT4 protein expression.

Adaptations, which might underlie the increased insulin sensitivity in trained individuals, include increases in levels of the glucose transporter protein GLUT-4 and in muscle glycogen synthase activity, a decrease in the serum triglyceride concentration and, possibly, an increase in the muscle capillary network.

In post absorptive humans, there are 100g of glycogen in the liver and 400g of glycogen in muscle. Carbohydrate oxidation by the working muscle can go up by 10-fold with exercise, and yet after 1 h, blood glucose is maintained at 4g. Blood glucose is preserved at the expense of liver and muscle glycogen. Liver glycogen breakdown protects blood glucose as the glucose moieties that comprise it are released into the blood. Muscle glycogen breakdown impedes the removal of glucose from the blood by increasing glucose 6-phosphate (G6P), which inhibits the hexokinase (HK) reaction, and by providing a source of fuel that diminishes the need for blood glucose. The amount of glucose in the blood can still be constant after 2 h of exercise in well-nourished subjects. Blood glucose is protected by liver gluconeogenesis after glycogen stores become critically low. Only after extremely prolonged exercise does blood glucose fall to concentrations that result in hypoglycemia severe enough to cause neuroglycopenia[44].

Glucagon is the primary controller of hepatic glucose production in the sedentary state [45]. Exercise is a robust challenge of the processes involved because of the high rates of glucose production necessary to maintain blood glucose[44]. Glucagon secretion from the pancreatic α cell increases during exercise, whereas insulin secretion from the pancreatic β cell declines. The decline in insulin secretion potentiates the actions of glucagon [46–48]. Studies in animals [49–51] and humans [46,52] demonstrate that the increase in glucagon is the primary stimulator of hepatic glucose production during exercise. The powerful effect of glucagon on hepatic glucose production was recently demonstrated by Berglund et al. [53]. This study showed that increasing glucagon in sedentary mice to levels similar to those seen during exercise causes a marked discharge of hepatic energy stores so that the adenosine monophosphate (AMP) to adenosine triphosphate (ATP) ratio is increased. This increase in the AMP: ATP ratio, through allosteric mechanisms, facilitates the glucagon-induced breakdown of glycogen and the oxidation of fat in the liver [51,54].

The translocation of GLUT4 from an intracellular vesicle to the plasma membrane and T tubules is a major mechanism through which both insulin and exercise increase skeletal muscle glucose transport. Contractile activity can stimulate GLUT4 translocation in the absence of insulin, and some studies suggest there are different intracellular "pools" of GLUT4, one stimulated by insulin and one stimulated by exercise [55]. These findings have provided the basis for our understanding of the glucose transport system with exercise in skeletal muscle.

Conclusion

Systematic review of literature indicates that regular participation in moderately intense physical activity is associated with a substantially lower risk of type 2 diabetes. The association was partly independent of BMI, suggesting that moderate-intensity physical activity can reduce the risk of type 2 diabetes even in those who do not achieve weight loss [56–58]. Findings from several prospective studies [59–62] indicate that 30 min or more of daily moderate-intensity activity, as recommended in multiple guidelines [63,64] can substantially reduce the risk of type 2 diabetes as compared with being sedentary. Moderately intense activity as defined in guidelines (3.0–6.0 MET h) includes walking at brisk pace but not walking at an easy or casual pace [65] and walking at brisk pace also seems preferable for the prevention of type 2 diabetes [61,66–70]. Further studies are needed to define more specifically what combinations of duration and pace are optimal for reducing the risk of type 2 diabetes. However, given that only a low percentage adults in the industrialized countries currently meet the general physical activity recommendations, efforts to prevent type 2 diabetes should strongly emphasize the benefit of moderately intense physical activities and encourage wider participation in these activities.

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