Molecular signaling mechanisms that mediate exercise training effects on insulin sensitivity

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Abstract Studies on exercise-induced stimulation of glucose uptake into skeletal muscle have indicated that components of the insulin signal transduction system, such as insulin receptor, IRS-1, and PI 3-kinase, are not involved in the mechanism of glucose uptake elicited by an acute bout of exercise, suggesting that the underlying molecular mechanism, by which an acute bout of exercise increases glucose uptake, is distinct from that of insulin. Sedentarism, maturation and dietary factors such as high-fat feeding cause insulin resistance, which is a result of defective signal transduction. On the other hand, exercise training and calorie restriction improve and prevent insulin resistance. The exercise training effects represented by improved insulin action in vivo are chiefly attributed to changes in body composition factors such as increased muscle volume and decreased body fat, and changes in post-insulin receptor mechanisms.

Keywords : insulin sensitivity, exercise training, skeletal muscle, glucose uptake, obesity

Introduction

It is well established that insulin sensitivity is exacerbated by sedentarism and obesity. On the other hand, insulin sensitivity in skeletal muscle increases with exercise training and calorie restriction, particularly when accompanied by weight loss. The exercise training effects represented by improved insulin action in vivo are chiefly attributed to changes in body composition factors such as increased muscle volume and decreased body fat, and changes in post-insulin receptor mechanisms¹⁻³⁾(Fig. 1). This review provides a contemporary perspective of our understanding of molecular and cellular events that occur in skeletal muscle in response to exercise, including its acute and chronic effects.

Molecular mechanisms of insulin- and exercise-stimulated glucose uptake

Insulin and exercise are the two most physiologically relevant stimulators of skeletal muscle glucose uptake, increased by translocation of glucose transporter 4 (GLUT4). In skeletal muscle, insulin stimulation results in the rapid phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1) on tyrosine residues and activation of phosphatidylinositol 3-kinase (PI 3-ki-

Fig. 1 Insulin receptor (A), IRS-1 (B), and PI 3-kinase (C) protein levels in rat gastrocnemius muscle. Values are the mean $\pm$ SE for 7 rats. (□) Sedentary rats; (■) trained rats. †Significantly different vs sedentary rats at 4 weeks ($P < .0083$)¹⁾.

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nase). Downstream of PI 3-kinase, the protein kinases Akt and atypical protein kinase c (aPKC) have been identified in mediating insulin-stimulated GLUT4 translocation⁴⁾.

Exercise increases AMP-activated protein kinase (AMPK) activity, leading to changes in glucose uptake⁵⁾. However, inhibition of AMPK has little or no effect on contraction-induced glucose uptake⁶⁾. Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII)⁷⁾ and LKB1⁸⁾ are upstream regulators of AMPK.

Chronic effects of exercise training on insulin signaling molecules

It is well established that exercise training improves insulin sensitivity⁹⁾. The exercise effects, represented by improved insulin action in vivo, are chiefly attributed to changes in body composition factors such as increased muscle volume and decreased body fat, increased blood flow to the exercising muscles, and changes in the post-insulin receptor mechanisms. GLUT4 protein expression also increases in response to exercise training, facilitating glucose uptake into trained muscles¹⁰⁾. We have reported that exercise training prevents maturation-induced decreases in insulin sensitivity, and suggested that the improvement in insulin sensitivity elicited by exercise training was in part attributed to an increase in insulin-sensitive GLUT4 on the plasma membrane¹¹⁾, and to the maintenance of IRS-1 and PI 3-kinase¹⁾ (Fig. 1) in rat skeletal muscle. GLUT4 protein expression increased in muscles of wild type mice after repeated treatment with the AMPK agonist AICAR, but it did not change in peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α)-knockout mice¹²⁾. Thus, the molecular basis for the exercise training-mediated improvement in glucose transport is attributable, at least in part, to PGC-1 α .

Effects of calorie restriction combined with exercise training on insulin sensitivity

In obese humans, calorie restriction and exercise training improve insulin sensitivity^{13,14)}. Sedentarism and obesity lead to insulin resistance, mainly through fat-derived adipocytokines. Fatty acid have been shown to cause a reduction in glucose uptake after insulin stimulation¹⁵⁾. Tumour necrosis factor- α (TNF- α) can impair IRS-1 docking to the insulin receptor, and this inhibits insulin signaling¹⁶⁾. Exercise training alone, and in combination with diet-induced weight loss, enhances mRNA expression of adiponectin receptors, but only calorie restriction-induced weight loss increases the levels of circulating adiponectin in obese¹⁷⁾. Thus, weight loss-induced improvement in insulin sensitivity is chiefly attributed to changes in adipocytokines.

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