Mechanisms underlying alterations in glucose metabolism due to exercise

Mayumi Takagi and Yasuko Manabe*

Department of Health Promotion Sciences, Graduate School of Human Health Sciences, Tokyo Metropolitan University, 1-1 Minami-Osawa, Hachioji, Tokyo 192-0397, Japan

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Abstract Exercise is known to affect glucose metabolism in healthy and diabetic individuals. Recent studies have demonstrated that both acute and chronic exercise improve glucose metabolism via several mechanisms. Acute exercise increases glucose uptake through activation of AMP-activated protein kinase with an increase in the intracellular AMP/ATP ratio, and also increases insulin sensitivity, possibly through TBC1 domain family member 4 regulation in the post-exercise period. Exercise also affects other organs in addition to skeletal muscle. Chronic exercise affects insulin secretion from the pancreas in response to glucose stimulation. This review describes how acute or chronic exercise regulates glucose metabolism. Although the detailed mechanisms remain unclear, these pathways might explain why exercise improves whole-body glucose metabolism.

Keywords: glucose metabolism, AMPK, insulin sensitivity

Introduction

It is well known that regular exercise has positive effects on the maintenance and improvement of whole-body glucose metabolism. DeFronzo showed that skeletal muscle contributes 70% of glucose disposable in the whole body1); therefore, skeletal muscle is directly involved in the maintenance of whole-body glucose metabolism. In general, alteration in glucose metabolism as a result of exercise is associated with the adaptive response of increased muscle mass. Interestingly, the improvement in glucose metabolism resulting from exercise is not always related to the alteration of body composition2), and research has revealed that an acute contraction is sufficient to stimulate glucose uptake in skeletal muscle3,4).

This review summarizes three important mechanisms of glucose metabolism: 1) glucose transporter 4 (GLUT4) translocation via exercise-induced activation (muscle contraction) of AMP-activated protein kinase (AMPK) in skeletal muscle and 2) improvement of insulin sensitivity following exercise in skeletal muscle. It also discusses the adaptive response of the pancreas with chronic exercise, that is, 3) chronic exercise-induced enhancement of insulin secretion in response to a high dose of glucose.

Mechanisms of glucose metabolism

GLUT4 translocation via AMPK activation by muscle contraction in skeletal muscle. Glucose is transported from the extracellular space into skeletal muscle cells through GLUT4. GLUT4 is generally pooled in intracellular vesicles but translocates to the plasma membrane in response to two major stimuli, insulin and muscle contractions. Despite the fact that both stimuli enhance GLUT4 translocation to the plasma membrane, the signaling pathways that activate this translocation differ from one another (Fig. 1). The findings for the insulin signaling pathway, which has been well documented, suggest that the binding of insulin to its receptor induces the activation of downstream signaling molecules, including phosphoinositide 3-kinase (PI3-K), insulin receptor substrate 1(IRS-1), and Akt, which eventually results in GLUT4 translocation5). Muscle contraction has no effect on the insulin signaling pathway, but activates an AMPK-dependent signaling pathway6). Muscle contraction leads to an increase in the intracellular AMP/ATP and ADP/ATP ratios in skeletal muscle. Allosteric binding of AMP or ADP to an AMPK molecule induces a conformational change, which induces phosphorylation of AMPK by the upstream kinase of LKB1, a constitutively active molecule. Ca^{2+}/calmodulin-dependent kinase kinases (CaMKKs) also activate AMPK7,8). In addition to AMPK, sucrone nonfermenting AMPK-related kinase (SNARK) is reported to be another downstream target of LKB1 for regulating glucose transport9). These events activate downstream signaling molecules such as TBC1 domain family member 1 (TBC1D1), a Rab-GTPase activating protein, and TBC1 domain family member 4 (TBC1D4/AS160), which results in GLUT4 translocation to the plasma membrane and an increase in glucose transport10).

In type II diabetes patients, the insulin signaling pathway is impaired, and therefore the blood glucose level is
increased. Interestingly, glucose uptake in skeletal muscle as a result of bicycle exercise is intact in type II diabetes subjects\(^1\), suggesting that the signaling pathway for glucose uptake stimulated by muscle contraction is intact in these subjects. Therefore, the contraction-stimulated pathway for glucose uptake has attracted the attention of many scientists because of the clinical importance of type II diabetes treatment and new drug targets.

**Improvement of insulin sensitivity following exercise in skeletal muscle.** Another important mechanism is the potent and sustained effect of exercise on insulin sensitivity in skeletal muscle. During physical activity, when one leg was exercised and the other was at rest, glucose uptake, stimulated by a submaximal concentration of insulin in the exercised leg, was significantly higher than that in the rested leg in humans\(^2\) and rodents\(^3\). Muscle contraction itself enhances glucose uptake independent of insulin signaling, but the effect of contraction-induced glucose uptake disappears within a few hours. Interestingly, the glucose uptake in exercised rat muscle was found to be higher than that in the rested muscle when rats were stimulated by insulin at 2.5 h following exercise (when the contraction-induced glucose transporters had already disappeared)\(^4\), suggesting that acute contraction has effects within the insulin signaling pathway. It is unclear which signaling molecules are involved in the enhancement of insulin sensitivity following exercise. TBC1D4 and TBC1D1 are suggested as possible molecules. Both are downstream of Akt and considered to be crucial molecules for GLUT4 trafficking. Both TBC1D4 and TBC1D1 are phosphorylated following exercise and by insulin administration. In particular, TBC1D4 is considered to be important, since it is additively phosphorylated by both insulin and muscle contraction\(^5\). In addition, TBC1D4 phosphorylation is retained 3-4 h following exercise\(^6,7\). These data suggest that TBC1D4 may play a role in improved insulin sensitivity following exercise.

**Chronic exercise-induced enhancement of insulin secretion in response to a high dose of glucose.** It is well accepted that chronic exercise leads to an increase in skeletal muscle mass and affects glucose metabolism\(^8\), but there is more to it. Chronic exercise affects not only glucose uptake ability in skeletal muscle but also insulin secretion ability stimulated by glucose in the pancreas. Pancreatic beta cells sense glucose levels in circulating blood and secrete insulin when the glucose levels are increased. Increased glucose (e.g., after a meal) is transported to the beta cells of islets via glucose transporter 2 (GLUT2), following which glucose metabolism is enhanced and the ATP/ADP ratio is increased in beta cells. Increased ATP

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**Fig. 1** Signaling pathway of glucose transporter 4 (GLUT4) translocation in skeletal muscle stimulated by insulin and exercise. Insulin phosphorylates the insulin receptor, which induces a cascade of phosphorylation of signaling molecules such as insulin receptor substrate 1 (IRS-1), phosphoinositide 3-kinase (PI3-K), and Akt, and results in the translocation of GLUT4 to the plasma membrane. Muscle contraction increases the AMP/ATP and ADP/ATP ratios. Binding of AMP or ADP to AMP-activated protein kinase (AMPK) induces an allosteric conformational change, which induces phosphorylation of AMPK by the upstream kinase of LKB1. Ca\(^2+\)/calmodulin kinase kinase (CaMKK) is also an upstream regulator of AMPK. Sucrose nonfermenting AMPK-related kinase (SNARK) is another downstream molecular of LKB1, which regulates glucose transport. These molecular events activate downstream signaling molecules such as TBC1 domain family member 4 and induce GLUT4 translocation to the plasma membrane\(^9\).
induces closure of ATP-sensitive potassium channels (K\textsubscript{ATP} channels) and induces depolarization of the beta cell membrane, which activates voltage-sensitive Ca\textsuperscript{2+} channels (VDCCs) and causes insulin granule exocytosis (Fig. 2).

In general, trained subjects have a lower plasma insulin level than sedentary subjects. This phenomena is considered to come from an increase in insulin sensitivity in peripheral tissues due to the effects of repetitive exercise, which consequently reduces the required insulin level necessary to maintain glucose homeostasis\textsuperscript{18-20}. There have been inconclusive results regarding whether exercise training enhances insulin secretion stimulated by glucose, because previous studies have used different methods and subjects, such as a hyperglycemic clamp\textsuperscript{21,22}, isolated islets\textsuperscript{23,24}, a cell-based assay\textsuperscript{25}, or an isolated islet perfusion assay\textsuperscript{26,27}. Convincing evidence regarding insulin secretion potential without any influence from the extracellular environment might be obtained using the isolated islet perfusion assay. We recently found that more than 6 weeks of treadmill training enhances insulin secretion stimulated by glucose\textsuperscript{28} (Fig. 3). Enhancement of insu-

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**Fig. 2** Secretion mechanism of insulin in beta cells. Glucose is transported from the extracellular space into beta cells via glucose transporter 2 (GLUT2). Increased intracellular ATP concentration resulting from glucose oxidation closes ATP-dependent K\textsuperscript{+} channels, which results in membrane depolarization. Membrane depolarization of beta cells opens voltage-dependent Ca\textsuperscript{2+} channels, which induces insulin secretion.

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**Fig. 3** Insulin secretion stimulated by glucose in trained and sedentary rats. Rats were trained for 6, 9, or 12 weeks. The islets were isolated after the training periods and placed on gel in the syringe column. Insulin secretion was studied by the perifusion of the islet cells stimulated by glucose. The graph is referenced from Tsuchiya M, et al. and has been modified by the authors.
lin secretion from islets of trained rats was observed on stimulation not only by glucose, but also by potassium, a membrane-depolarizing agent, suggesting that the downstream signals of membrane depolarization are sensitized by chronic exercise. Although we do not have conclusive results describing which mechanism is involved in the enhanced insulin secretion potential in trained rat islets, one possible explanation emerges from the recent data about the relationship between glucagon-like peptide-1 (GLP-1), known as a stimulator of insulin secretion (incretin), and interleukin-6 (IL-6). IL-6 is a myokine and its concentration in plasma is elevated as a result of exercise. IL-6 facilitates GLP-1 production by acting on intestinal L cells and the pancreatic alpha cells.

Exercise improves whole-body glucose metabolism via increased glucose uptake to skeletal muscle, increased insulin sensitivity, and increased insulin secretion stimulated by glucose. Although the details of these mechanisms remain unclear, exercise has much more potential for influencing glucose metabolism than was thought possible earlier.

**Conclusion**

Exercise improves whole-body glucose metabolism via increased glucose uptake to skeletal muscle, increased insulin sensitivity, and increased insulin secretion stimulated by glucose. Although the details of these mechanisms remain unclear, exercise has much more potential for influencing glucose metabolism than was thought possible earlier.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

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