Diverse Signals Regulate Glucose Uptake into Skeletal Muscle

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ABSTRACT

Skeletal muscle glucose uptake is mediated by glucose transporter 4, the major isoform that is responsive to hormones such as insulin, and by energy-demanding conditions such as exercise and hypoxia. While participation of the phosphatidylinositol 3-kinase (PI3K) pathway in insulin-stimulated glucose uptake is well established, the signals involved in mediating glucose uptake in response to exercise and hypoxia (collectively termed "alternative pathway" since it is PI3K-independent) are largely unknown. 5'-AMP-activated kinase (AMPK) and Ca^{2+} have been implicated in these insulin-independent pathways, but their exact contribution is being debated. The evidence for diverse signalling pathways regulating glucose uptake in response to these stimuli that engage the "alternative pathway" is reviewed.

RÉSUMÉ

La captation du glucose par le muscle squelettique est assurée par le transporteur 4 du glucose, l'importante isoforme sensible aux hormones telle l'insuline, et par des situations qui exigent beaucoup d'énergie, tels l'exercice et l'hypoxie. Le rôle de la voie de la phosphatidylinositol 3-kinase (PI3K) dans la captation du glucose stimulée par l'insuline est bien établi, mais les signaux qui interviennent dans la médiation de la captation du glucose en réponse à l'exercice et à l'hypoxie (collectivement appelés «voie alterne» car ils sont dépendants du PI3K) sont en grande partie inconnus. La kinase activée par la 5'-AMP (AMPK) et le Ca^{2+} ont été associés à ces voies insulinodépendantes, mais leur rôle exact est controversé. Dans ce compte rendu, les auteurs passent en revue les données sur les diverses voies de signalisation qui régissent la captation du glucose en réponse aux stimuli qui intéressent la «voie alterne».

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INTRODUCTION

Insulin-stimulated glucose uptake by skeletal muscle plays an important role in the maintenance of whole-body glucose homeostasis. Glucose transporter 4 (GLUT4) is the main glucose transporter isoform expressed in skeletal muscle that mediates glucose uptake in response to hormones such as insulin, to stimuli such as exercise/contraction and hypoxia, and to pharmacological interventions that alter mitochondrial energy output. Under basal conditions, GLUT4 is predominantly sequestered in several intracellular compartments. Both insulin and muscle contraction cause a net gain of GLUT4 at the plasma membrane to increase glucose uptake, but they utilize distinct signalling molecules and mobilize GLUT4 from different intracellular pools.

It is well accepted that activation of the insulin receptor substrates (IRS)/phosphatidylinositol 3-kinase (PI3K) axis is indispensable to insulin-stimulated GLUT4 translocation and glucose uptake. Similarly, it is well documented that 2 serine/threonine kinases (Akt and the atypical protein kinase C [aPKC] zeta/lambda downstream of PI3K) participate in mediating insulin's metabolic actions in skeletal muscle and fat. Recent evidence also suggests that in adipose cells, c-Cbl-associated protein (CAP), adaptor protein associated with pleckstrin homology and Src homology2 (SH2) domain (APS) and the small GTPase TC10 may also be involved in mediating insulin regulation of GLUT4 traffic and glucose uptake.

However, the molecular mechanisms by which muscle contraction/hypoxia increase glucose uptake are less well defined, although they appear to be independent of the PI3K pathway. Most intriguing is the observation that the recently identified hormone adiponectin also stimulates skeletal muscle glucose uptake in a PI3K-independent manner. Here we will highlight the evidence that implicates the "alternative pathways" utilized by muscle contraction, hypoxia, the mitochondrial uncoupler 2,4-dinitrophenol (DNP) and adiponectin to stimulate glucose uptake in skeletal muscle and muscle cells in culture. Understanding these "alternative pathways" utilized by the listed stimuli could be of great value in bypassing defects in glucose transport that arise in insulin resistance.

It is beyond the scope of this review to discuss the insulin-signalling cascade. Readers are referred to extensive reviews on this topic (1,2) and to a review on the signalling defects associated with insulin resistance (3). Although there is an array of adipokines that reportedly modulate insulin sensitivity and play a role in insulin resistance associated with obesity and type 2 diabetes, we have focused on adiponectin because it is found to have a positive effect on glucose uptake in skeletal muscle and muscle cells in culture. Nonetheless, more work is required to explore the effects of these adipokines on glucose uptake, especially as new ones are identified.

"ALTERNATIVE PATHWAYS" LEADING TO GLUCOSE UPTAKE

Exercise/muscle contraction stimulates glucose uptake into skeletal muscle independently of insulin or PI3K activity (Table 1). However, the mechanisms by which exercise/contraction regulates glucose uptake are not well understood. As with exercise, hypoxia also enhances glucose transport into skeletal muscle and muscle cells in culture (Table 1). Although hypoxia was initially proposed as an experimental model for exercise-induced glucose uptake, it is now clear that each stimulus may engage distinct signals to achieve a common goal. Hypoxia is imposed on isolated cells or isolated skeletal muscle by oxygen deprivation and its effects are mimicked by pharmacological interference with the mitochondrial oxidative chain. DNP is a mitochondrial uncoupler that transiently reduces cellular adenosine triphosphate (ATP) levels. DNP stimulates glucose uptake into both L6 myotubes (Figure 1A) (4) and isolated fast-twitch muscle (Figure 1B) independently of PI3K activity (5). Hence, exercise, hypoxia and DNP are said to engage "alternative" signalling pathways.

Role of 5'-AMP-activated protein kinase (AMPK) in the stimulation of muscle glucose uptake

The heterotrimeric enzyme AMPK has been proposed as an "energy sensor" that is rapidly phosphorylated and activated during exercise/contraction in skeletal muscle (6,7). As muscle glucose transport correlated well with AMPK activity, it was proposed that AMPK might be a signal in exercise/contraction-stimulated glucose transport into skeletal muscle (8,9). Consistent with this correlation, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), a pharmacological activator of AMPK, stimulates glucose uptake into fast-twitch muscle (Table 1, Figure 1B) (8,9). AICAR-induced glucose uptake, albeit lower than that elicited by muscle contraction, is insensitive to PI3K inhibitors and is additive to that of insulin (8,9). Hypoxia and DNP also increased AMPK activity in L6 myotubes (10) and in isolated skeletal muscle (11), providing further support for a link between AMPK activation and glucose uptake.

However, several strategies that tested the possible involvement of AMPK in the stimulation of glucose uptake yielded little support for the original hypothesis. Early on, it was observed that chelation of intracellular Ca^{2+} in L6 myotubes reduced DNP-stimulated glucose uptake without affecting AMPK activity (10). This observation suggested that another Ca^{2+}-dependent event is involved in the stimulation of glucose uptake, parallel to or downstream of AMPK. Similarly, a dissociation between exercise-stimulated glucose uptake and AMPK activity in slow-twitch muscle has been observed (12).

More direct challenges to the connection between AMPK and contraction-stimulated glucose uptake have recently emerged. AMPK consists of a catalytic subunit (alpha1 and alpha2 isoforms) and 2 regulatory subunits (beta1, beta2 and gamma1, gamma2, gamma3). The alpha1 subunit is