Cellular and molecular regulation of cardiac glucose transport

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Metabolic imaging is used to differentiate viable ischemic myocardium from regions of necrosis in patients with ischemic heart disease and left ventricular dysfunction. Myocardial uptake of the glucose analogue fluorodeoxyglucose (F-18) (FDG) has been assessed with positron emission tomography[1] and more recently with single photon emission computed tomography.[2] The cellular uptake of glucose or its analog FDG across the sarcolemma membrane is mediated by glucose transport proteins (GLUTs), which facilitate the movement of glucose across the otherwise impermeable lipid membrane. Glucose transport is the rate-limiting step in myocardial glucose uptake under basal conditions[3]; therefore stimulation of glucose uptake requires an increase in glucose transport across the sarcolemma. The regulation of glucose metabolism in the heart has been reviewed recently.[4] This article reviews the current understanding of the cellular and molecular regulation of cardiac glucose transport and transport proteins and examines recent research on potential novel mechanisms that regulate glucose transport.

Glucose Transporter Family

There are two classes of glucose transporters: the sodium-glucose cotransporter and the facilitative glucose transporters. The cotransporter, which is not present in heart, uses the inward sodium gradient as an energetic mechanism to drive glucose transport and efficiently absorb glucose in the intestine. The facilitative glucose transporters, the topic of this review, simply mediate glucose entry, driven by the inward glucose gradient. These transporters are 50-kd integral membrane proteins that contain 12 membrane-spanning domains and 6 extracellular loops, including a glucose-binding site on the large first exofacial loop. They have important amino acid sequences in both the NH_2 and COOH cytoplasmic domains, which regulate transporter movement within the cell (Figure 1). There are 5 members of the glucose transport family, GLUT1 to 5, which are the products of distinct genes rather than splice isoforms.[5] However, only 4 of these proteins (GLUT1 to 4) are known to actually function as glucose transporters. GLUT1 and GLUT4 are the important isoforms present in the heart.

GLUT1 is a relatively ubiquitous transporter found in the plasma membrane in many tissues, including the heart, and accounts for the bulk of basal glucose uptake.[6] However, the amount of GLUT1 expressed in the heart is regulated by stress,[7] and GLUT1 is also present and recruitable from intracellular membrane storage pools.[8,9] The GLUT2 transporter is present in the liver, kidney, pancreas, and intestine.[10] GLUT3 is present in neuronal tissues but has also been reported in skeletal muscle and heart.[11] GLUT4 is the classic insulin-stimulated glucose transporter and is present in heart, skeletal muscle, and fat.[12] Under nonstimulated conditions, GLUT4 resides to a large extent within intracellular storage vesicles and makes only a small contribution to glucose uptake. However, GLUT4 plays an extremely important role in heart and skeletal muscle under stimulated conditions, such as hyperinsulinemia or energetic stress.[13] GLUT4 is recruited or "translocated" to the plasma membrane with insulin stimulation,[9,14,15] exercise,[16] hypoxia,[17] and ischemia.[8,14] The mechanisms regulating the translocation of GLUT4 have been the subject of intensive investigation and will be discussed in detail. GLUT5 is present in the small intestine[10] but appears to function primarily as a fructose transporter.[18]

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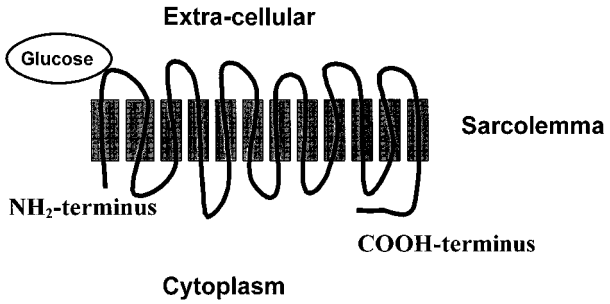

Figure 1. Schematic representation of GLUT4 in the sarcolemma with 12 membrane-spanning domains and 6 exofacial loops, including a glucose-binding site.

Mechanisms Regulating Glucose Transporter Activity

The rate of glucose transport is determined by the transmembrane glucose concentration gradient and the overall number, subcellular distribution, and intrinsic kinetic activity of glucose transporters.

The intracellular concentration of glucose is normally very low.[19] The inward transmembrane concentration gradient is the driving force for glucose entry into the cell. The facilitative glucose transporters present in the heart (GLUT4 and GLUT1) simply mediate the movement of glucose down its concentration gradient. Therefore high extracellular glucose concentrations drive glucose transport, whereas low extracellular concentrations, which occur during hypoglycemia or ischemia,[20] decrease glucose flux into the cell.

The overall content of glucose transporters in the sarcolemma membrane is a function of both the number of transport proteins expressed in the cell and the subcellular distribution of those proteins between the sarcolemma membrane and intracellular storage membranes. The overall number of transporters present in the cell reflects the rate of gene transcription, mRNA stability, and rates of protein translation and degradation.[21] The most important mechanism regulating the cellular content of GLUT4 appears to be the rate of transcription. However, changes in the content of glucose transporters occur relatively slowly and do not occur within the time frame of acute insulin or ischemic stimulation. Nonetheless, changes in GLUT content may be an important mechanism for more long-term regulation of glucose transport.

The primary mechanism involved in the acute activation of glucose transport is the redistribution of glucose transporters from the intracellular pool to the sarcolemma, which is known as translocation.[22] Translocation primarily involves the outward movement of transporters to the cell membrane but to some extent may also reflect a decrease in the rate of endocytosis or recycling of glucose transporters into the intracellular storage pool.[23]

Finally, membrane transporters may be activated by phosphorylation of their component amino acids by protein kinases. GLUT4 undergoes phosphorylation of its COOH terminal end in response to catecholamine stimulation in adipocytes,[24,25] although this phosphorylation does not appear to influence translocation of the transporter. However, recent studies indicate that inhibition of the mitogen-activated protein (MAP) kinase, p38 MAP kinase, decreases insulin-stimulated glucose transport without influencing the translocation of GLUT4, indicating the potential importance of GLUT4 phosphorylation in modulating transport activity.[26]

Subcellular Localization of Glucose Transporters

Acute activation of glucose transport is mediated by the recruitment of GLUTs from intracellular storage membranes to their physiologically active site on cell surface membranes where they facilitate glucose entry into the heart. The sarcolemma appears to be the primary site to which cardiac glucose transporters are targeted. However, glucose transporters are known to undergo translocation to the T tubules in skeletal muscle[27] and to some extent in the heart.[28] The T tubules are invaginations of the surface membrane that may provide delivery of glucose deep into the myocyte.

A key to studying the regulation of glucose transport in the heart are the techniques that define the cellular and subcellular localization of cardiac GLUTs. The differentiation of GLUTs in cardiomyocytes from those in other cells in the heart, such as fibroblasts and endothelial cells, is also important for understanding the physiology of glucose transport.

Several experimental approaches have been used in recent years. One method involves fractionation of cells, separation and purification of membrane components, and subsequent quantification of transporters by immunoblotting with specific GLUT antibodies. This approach estimates the amount of glucose transporter in the sarcolemma and in intracellular storage vesicles.[8,14] A second technique involves biochemically labeling surface glucose transporters with impermeant compounds that bind with some selectivity to plasma membrane glucose transporters.[29] After immunoprecipitation with specific glucose transporter antibodies, the labeling of specific isoforms of the glucose transporter can be quantified.[30]

Cellular imaging modalities have also provided important insights into the cellular and subcellular distribution of glucose transporters. Specific antibodies are bound to glucose transporters in myocardial sections or intact cells and then are labeled with probes, which can

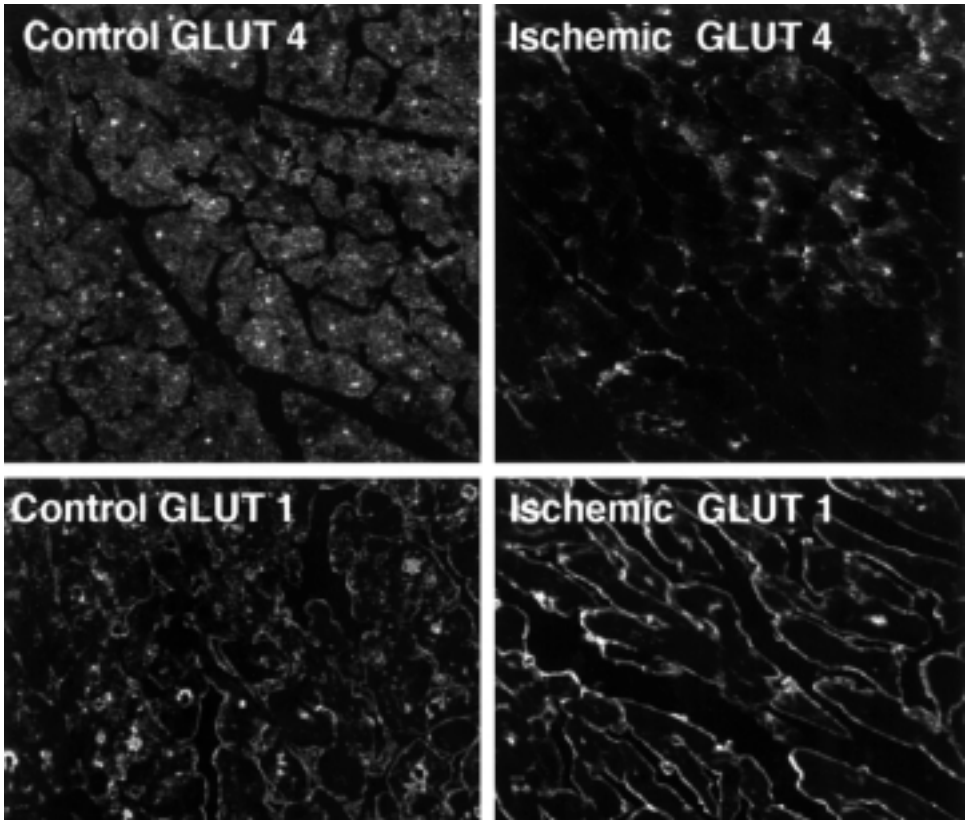

Figure 2. Immunofluorescence images of GLUT4 and GLUT1 in control and ischemic myocardial regions during moderate low-flow ischemia. Modified with permission from Young et al.[13]

be visualized with confocal laser microscopy.[8] This is the cell biology equivalent of tomographic imaging, providing high-resolution, cross-sectional images. Antibodies can also be labeled with gold particles, which are directly visualized by electron microscopy with even greater precision than by light microscopic methods.[28] These methods demonstrate the association of glucose transporters with specific membrane domains and intracellular vesicular populations. In addition, in isolated cell systems, GLUT4 can be genetically tagged with protein sequences, which are easily identifiable with antibodies with green fluorescent protein, which is visualized with microscopy directly. This latter technique has provided dramatic visualization of the intracellular movement of GLUT4 in adipocytes,[31] where the lesser complexity of subcellular membranes and the lack of myofibrillar proteins render this analysis more feasible than in muscle tissue.

Glucose Transport During Myocardial Ischemia

Early studies demonstrated that myocardial ischemia increases the glucose transport activity of sarcolemma membranes. Before the advent of modern immunologic techniques that identified specific glucose transporters, hypoxia was shown to increase the content of proteins in the sarcolemma that bind radiolabeled cytochalasin B, a fungal metabolite that binds to glucose transporters.[32] After GLUT4 and GLUT1 were cloned and sequenced, specific antibodies were developed, which have been used to demonstrate that hypoxia stimulates GLUT4 translocation in skeletal muscle.[17] Subsequently, GLUT4 translocation was also observed in the retrogradely perfused rat heart subjected to global ischemia.[14]

We have demonstrated that GLUT4 and GLUT1 transporters undergo translocation to the sarcolemma membrane in the intact canine heart during regional ischemia.[8] Glucose uptake is increased 2- to 3-fold by ischemia in this model, where residual glucose delivery is only modestly diminished. Immunoblotting revealed an increase in sarcolemmal GLUT4 and GLUT1 content with a decrease in the concentrations of these transport proteins in the intracellular membrane pool.[8] Immunofluorescence showed little surface membrane GLUT4 in the nonischemic region but significant sarcolemma GLUT4 localization in the ischemic region (Figure 2).[8,13] In addition, these studies demonstrated

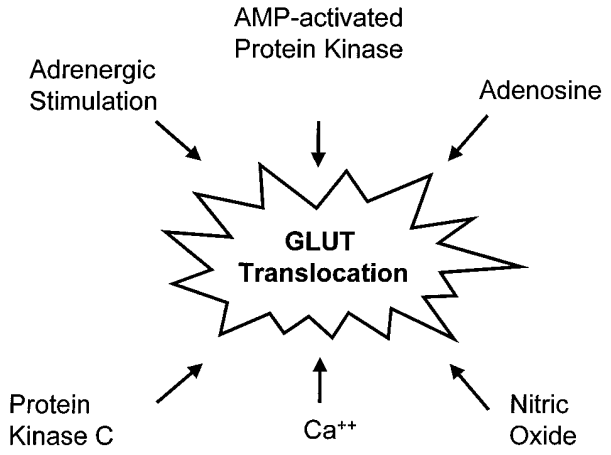

Figure 3. Potential mediators of GLUT translocation in the ischemic heart. *AMP*, Adenosine monophosphate.

predominant sarcolemma GLUT1 localization, which is mildly increased in the ischemic heart. Further studies by our laboratory demonstrated the additive effects of insulin and ischemia on GLUT translocation in this model.[15]

Signal Transduction Pathways and Glucose Transporter Translocation

Several stimuli lead to the translocation of glucose transporters.[13,33] Probably the most important stimuli in the heart are insulin, ischemia, exercise, and catecholamines. The molecular mechanisms that are initially activated by these stimuli and ultimately lead to transporter translocation are referred to as signal transduction pathways. Recent research has led to several discoveries that have helped to define these pathways.[34]

The best understood pathways are those related to insulin stimulation of glucose transport. A substantial amount of work has been performed to define these pathways in the isolated adipocyte, and the results of these studies have direct relevance to the heart. Insulin-binding to its receptor leads to autophosphorylation of the receptor, subsequent binding and phosphorylation of insulin-receptor substrates (insulin-receptor substrate proteins), and then binding and activation of the p85/p110-type phosphatidylinositol 3-kinase (PI 3-kinase).[34] The interaction of these proteins is mediated by the binding of specific amino acid sequences and leads to the activation of the membrane-associated lipid kinase, PI 3-kinase, which appears to be necessary for GLUT translocation. Insulin-mediated GLUT4 translocation is blocked by inhibitors of this enzyme in the heart[35] and other tissues. The 2 potential downstream pathways activated by the polyphosphoinositide products of the reactions catalyzed by PI 3-kinase are protein kinase B or Akt[36] and the ζ-isoform of protein kinase C.[37] However, the mechanism by which these kinases lead to GLUT4 vesicular movement to the membrane remains an active and important area of investigation.

In contrast to the insulin-signaling pathway, much less is known about the signal transduction pathway(s) involved in ischemia and exercise.[38] The latter has been the focus of intense investigation by exercise physiologists and diabetologists because of the importance of exercise-mediated muscle glucose uptake in patients with diabetes. Inhibitors of PI 3-kinase such as wortmannin block insulin-stimulated glucose transport but do not block the stimulation of GLUT translocation during myocardial ischemia[35] or skeletal muscle contraction.[39] Therefore these stimuli do not appear to exert their effects on transporter translocation through PI 3-kinase.

Several potential mediators of glucose transporter translocation during conditions that cause "energetic stress" have been proposed (Figure 3). Possible signals include calcium,[40] nitric oxide,[41,42] bradykinin,[43] adrenergic stimulation,[44] MAP kinase activation,[45] protein kinase C,[46] and adenosine.[47] Although each of these signaling pathways may have some impact on transporter translocation, none has been consistently identified as the predominant mechanism.

Catecholamines stimulate glucose uptake and GLUT4 translocation in the heart[48] and may play a role in mediating transporter translocation during exercise and ischemia.[49] In isolated cardiomyocytes, their effect appears to be mediated primarily through the α-adrenergic receptor stimulation.[30] In the isolated perfused heart, both α- and β-adrenergic stimulation lead to increased glucose uptake[50] and GLUT translocation.[49]

Our laboratory has recently investigated the role of adenosine monophosphate-activated protein kinase (AMPK) as a potential novel mechanism, which signals glucose transporter translocation in the heart. AMPK is the mammalian homologue to the yeast SNF1 protein, which has an important role in that organism's usage of sugars.[51] AMPK has been described as a metabolic fuel gauge or energetic stress kinase that activates energy-generating fuel substrate pathways and turns off energy-consuming biosynthetic pathways.[52] AMPK regulates 3-hydroxy-3-methylglutaryl coenzyme A reductase in the liver, phosphorylating and inactivating this enzyme and thus inhibiting cholesterol biosynthesis.[53] More recent work has indicated that AMPK is important in the regulation of fatty acid oxidation in both skeletal muscle[54] and heart,[55] phosphorylating and inactivating acetyl-coenzyme A carboxylase. Inhibition of acetyl-coenzyme A carboxylase decreases the concentration of malonyl-

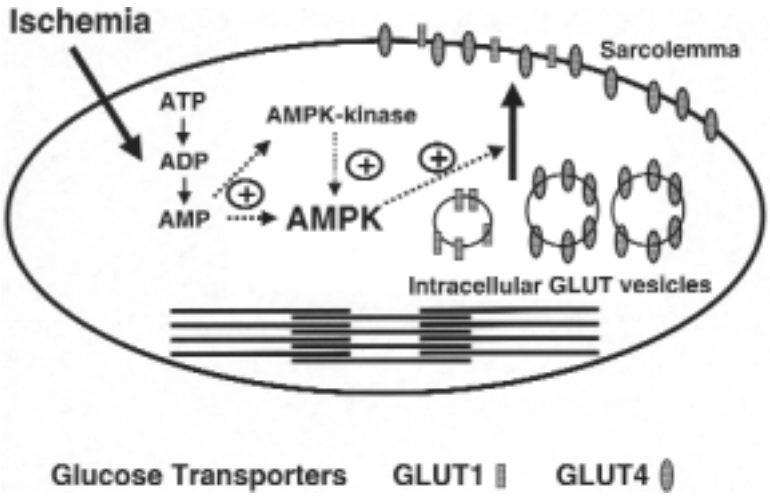

Figure 4. Adenosine monophosphate-activated protein kinase (*AMPK*) is activated by increases in the *AMP*/adenosine triphosphate (*ATP*) ratio in the ischemic heart, directly and through activation of the upstream kinase (*AMPK*) kinase, leading to GLUT translocation to the sarcolemma and increased glucose transport.

coenzyme A, which is an inhibitor of fatty acid oxidation; thus AMPK increases fatty acid oxidation.

AMPK is activated during myocardial ischemia[55] and muscle contraction[54] by an increase in the ratio of AMP to adenosine triphosphate (Figure 4). This direct activation is further amplified by the action of the upstream AMPK kinase, which phosphorylates and activates AMPK.[51] AMPK is also activated by a decrease in the creatine phosphate to creatine ratio.[56] This additional mechanism likely has an important role in the ischemic activation of this enzyme.

Our recent work has focused on the potential role of AMPK in the regulation of glucose transport in the heart. AMPK can be activated pharmacologically by the adenosine analog 5 aminoimidazole-4 carboxamide 1-β-D-ribofuranosamide (AICAR),[57] which was originally developed as a cardioprotective agent. AICAR is phosphorylated to its monophosphate, which functions as an AMP analog and activates AMPK. We found that AICAR increases deoxy glucose uptake in left ventricular papillary muscles of the rat to a level similar to insulin or chemical hypoxia.[58] This activation of glucose transport by AICAR is not blocked by wortmannin, indicating that AMPK acts independently from the insulin-signaling pathway or possibly distal to PI 3-kinase. Both immunolocalization and membrane fraction techniques indicated that AICAR stimulates the translocation of GLUT4 to the sarcolemma membrane.[58] Although specific inhibitors of AMPK are not currently available, kinase inhibitors, which inhibit AMPK, also block the stimulation of glucose transport by AICAR and chemical hypoxia.[58]

In addition, we have found that AMPK stimulation in vivo activates cardiac glucose transporter translocation in the intact organism.[59] The local intracoronary infusion of AICAR stimulates both GLUT4 and GLUT1 translocation to the sarcolemma. AMPK stimulation also increases myocardial glucose and free fatty acid uptake in the normal heart, the latter effect reflecting its known action to stimulate free fatty acid oxidation.[55] These findings support the contention that AMPK may be an important initial signal transduction mechanism, triggering the translocation of glucose transporters in the ischemic heart.[13] The downstream events mediating GLUT vesicular movement after AMPK activation remain to be defined.

Molecular Basis of Glucose Transporter Vesicular Trafficking

Glucose transporters cycle in and out of the sarcolemma, a process which is referred to as membrane vesicular trafficking. Most knowledge about GLUT4 trafficking has come from experiments performed in adipocytes, which are insulin-sensitive but have a much less complex membrane structure than cardiac cells. However even in this cell system, defining the subcellular membrane compartments through which GLUT proteins move and how the trafficking of these proteins is specifically and selectively regulated has been a major challenge.

When GLUT4 is not in the sarcolemma, it is found predominantly within discrete intracellular membrane vesicles, which are distinct from the constitutively recycling endosomal system.[60] The latter system cycles membrane proteins, including the transferrin receptor, the insulin-like growth factor-II/mannose 6-phosphate recep-

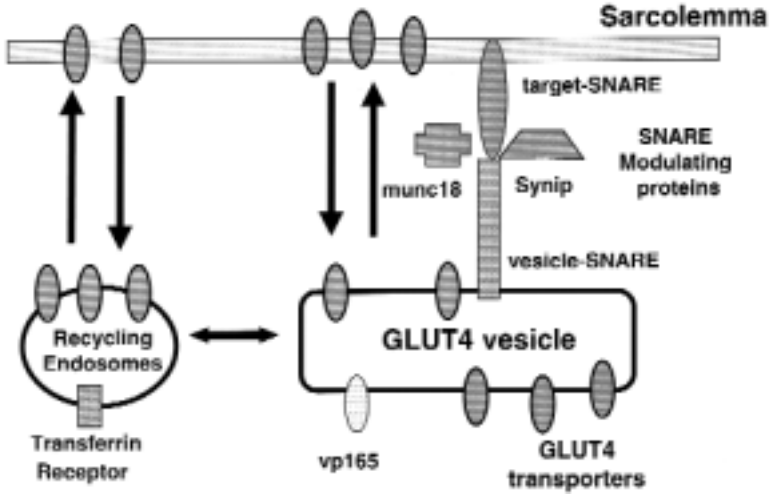

Figure 5. Schematic diagram of the postulated retention and synaptic models regulating glucose transporter vesicular trafficking. In the retention model, stimulation causes release of sequestered GLUT4 vesicles that enter the constitutively recycling endosomal pathway. In the synaptic model, GLUT4 translocation occurs as a result of interactions between v-SNARE and t-SNARE proteins and proteins that modulate these interactions.

tor and GLUT1, between the trans-Golgi network, plasma membrane, clathrin-coated endocytotic vesicles, and endosomes. Two current theories explain how GLUT4 trafficking is regulated and are sometimes referred to as the "retention model" and the "synaptic model."[60]

The retention model postulates that GLUT4 vesicles are sequestered from entering the constitutive recycling endosomal pathways in the basal state. However, on stimulation of the cell, these vesicles are released into the endosomal pathway and transit to the sarcolemma (Figure 5). GLUT4 vesicles are found in close proximity to endosomes.[61] In adipocytes, the insulin-responsive aminopeptidase, also known as vp165, colocalizes with GLUT4 vesicles;[62] disruption of its interaction with GLUT4 allows GLUT4 vesicles to enter the endosomal recycling pathway.[63] However, a substantial amount of GLUT4 does not colocalize with the endosomal pool, and experimental ablation of transferrin receptor-containing endosomes does not inhibit insulin-stimulated GLUT4 translocation.[64] Thus insulin-stimulated GLUT4 translocation can occur independent of the endosomal recycling compartment.

The synaptic vesicle model (Figure 5) postulates that specific intracellular membrane pools of GLUT4 exist and move to the target plasma membrane as the result of interactions between specific paired proteins located on these membranes.[60] This theory is based on the discovery of protein complexes that mediate the fusion of synaptic vesicles with presynaptic membranes, leading to neurotransmitter release. The paired proteins are vesicle soluble NSF attachment protein (SNAP) receptors (v-SNAREs) and target membrane SNAP receptors (t-SNAREs) whose interaction is modulated by SNAPs.[65] The recent identification of homologues in insulin-sensitive cells strongly suggests that SNARE proteins may be involved in the regulation of GLUT4 trafficking. A t-SNARE, syntaxin 1A/1B,[66] and a v-SNARE, cellubrevin,[9] are found in cardiac myocytes. In adipocytes, the proteolytic cleavage of cellubrevin, or vesicle-associated membrane protein (VAMP) 2, another v-SNARE, from these GLUT4 vesicles inhibits GLUT4 translocation, providing additional support for the importance of SNARE proteins in GLUT4 trafficking.[67]

The binding between v-SNAREs and t-SNAREs is a highly regulated process, modulated by additional proteins that either enhance or inhibit vesicular movement. These regulatory proteins were initially discovered in synaptic vesicles but their homologues are also being identified in insulin-sensitive tissues. SNAP25 modulates the interaction between syntaxin 1A and VAMP2[68]; although SNAP25 is not present in insulin-sensitive tissues, its homologue, syndet, has been identified in adipocytes.[69] The Munc family of proteins inhibits the interaction between SNARE proteins. Munc 18 reduces the binding of syntaxin 4 to VAMP2, so that overexpression of Munc 18 inhibits insulin-stimulated GLUT4 translocation.[70] In addition, insulin decreases the binding of Munc 18 to syntaxin 4, which may result in GLUT4 translocation. An additional insulin-regulated syntaxin 4-binding protein, synip, positively modulates SNARE protein interaction and hence GLUT4 translocation.[60]

Small guanosine triphosphate (GTP)-binding proteins that colocalize to GLUT4 vesicles and may also modulate GLUT4 translocation have been discovered. Nonmetabolizable GTP analogues induce GLUT4 translocation.[71] In adipose tissue and skeletal muscle, the GTP-binding protein, rab4, appears to have an important role in insulin-stimulated GLUT4 translocation.[60] Although this protein is not abundant in the heart, another GTP-binding protein, p24, has been found in the myocardium.[72] Insulin leads to the release of these GTP-binding proteins from intracellular vesicles into the cytoplasm, and this may have an important role in GLUT4 trafficking.

During times of energetic stress in the heart such as during exercise or ischemia, it might seem more efficient to limit endocytotic recycling of sarcolemmal GLUT4 rather than to increase the rates of GLUT4 movement to the sarcolemma. Endocytosis occurs by way of clathrin-coated pits, which are specialized regions of the plasma membrane. Disruption of these regions inhibits GLUT4 internalization.[73] The primary protein regulating synaptic endocytosis is the GTPase dynamin, which colocalizes with clathrin and cleaves budding endocytotic vesicles. Interference with dynamin function inhibits GLUT4 endocytosis[74] and leads to the accumulation of GLUT4 in the plasma membrane of adipocytes,[75] indicating that dynamin may have an important role in regulating GLUT4 endocytosis.

Regulation of GLUT Expression

The expression of glucose transporters is determined largely by the activity of GLUT gene transcription. Glucose transporter expression is highly regulated in terms of tissue specificity, changes during development, and alterations under a number of pathologic conditions.

GLUT gene transcription is under the control of a number of factors[21] that influence the activity of the GLUT4 and GLUT1 promoters directly or indirectly. The GLUT4 gene has an upstream 2.4 kilobase promoter element that appears to be critical for GLUT4 transcription.[76] The factors leading to the selective expression of GLUT4 in insulin-sensitive tissues (heart, adipocytes, and skeletal muscle) are only partially understood. The GLUT4 promoter sequence contains a myocyte enhancer factor 2-binding domain that is necessary, although not sufficient, to support GLUT4 transcription.[77] Myocyte enhancer factor 2 belongs to a family of transcriptional factors that have an established role in myogenesis. However, the traditional concept of selective expression of GLUT4 in insulin-responsive tissues has also been called into question by the identification of GLUT4 in other tissues, including the brain.[78] The factors mediating the expression of GLUT4 and the role of GLUT4 in such locations remain uncertain.

The embryonic and neonatal myocardium primarily express GLUT1,[79,80] but upregulation of GLUT4 and downregulation of GLUT1 in the postneonatal period lead to GLUT4 predominance in the normal adult heart.[81] In experimental models of diabetes, the expression of GLUT4[82] and GLUT1[83] is decreased in the heart. Whether this occurs as a result of hypoinsulinemia, hyperglycemia, or changes in cellular energetics and intracellular glucose concentrations remains unclear. The decrease in GLUT4 expression in experimental diabetes is related to decreased GLUT4 gene transcription.[84] In addition, fasting decreases GLUT1 expression in the rat heart and may occur as a result of low insulin levels or energy deprivation.[85]

Glucose transporter expression may also be altered in hypertrophy. A decreased ratio of GLUT4/GLUT1 expression has been reported in patients with left ventricular hypertrophy induced by aortic stenosis.[86] Although these studies have not examined the degree to which the recruitability of GLUT4 to the sarcolemma is compromised, these patients have decreased insulin-stimulated glucose uptake.

GLUT1 appears to be a stress protein whose expression is increased by a number of factors, including chronic hypoxia.[87] Interestingly, GLUT1 is likely regulated by the hypoxia-inducible factor-1α,[88] an important transcriptional factor in the heart and other tissues. In neonatal cardiocytes, GLUT1 transcription is also subject to regulation by alpha-adrenergic stimulation, which appears to be mediated by the activation of MAP kinases.[80] The upregulation of GLUT1 appears to have a beneficial effect in neonatal myocytes, where it prevents cardiac apoptosis during hypoxia.[89]

Genetic Modulation of Glucose Transporters in the Heart

Transgenic mice in which the expression of GLUT proteins has been manipulated provide novel insights into the role of glucose transport in the heart.[21] Several strains of mice have been created, including those that overexpress GLUT4[90] and mice with various degrees of GLUT4 deletion, such as the GLUT4 null mouse[91,92] and the cardiac-specific GLUT4 knockout mouse.[93]

GLUT4 transgenic mice have increased insulin-stimulated myocardial deoxy glucose uptake, supporting the importance of glucose transport in the heart.[90] GLUT4 null mice, which lack GLUT4 in heart, muscle, and fat, have marked cardiac hypertrophy and growth retardation and die prematurely.[91] These animals have altered glucose metabolism but surprisingly are not

diabetic because of hyperinsulinemia and the expression of a novel glucose transporter (GLUTx) in skeletal muscle. The hypertrophy observed in these mice may be a response to generalized energy depletion because these mice have decreased plasma free fatty acids, lactate, and ketones. Alternatively, the increases in plasma insulin may drive hypertrophy through changes in protein turnover. The heterozygous null mice have normal heart GLUT4 levels but also develop a cardiomyopathy. However, this cardiomyopathy may be the consequence of the hypertension and diabetes seen in these animals.[92]

The cardiac-specific knockout, in which GLUT4 is inactivated in the heart with the Cre-loxP gene recombination method, is not complicated by the changes in circulating substrates and hormones associated with the null mouse. Nonetheless, these mice also have a minor degree of cardiac hypertrophy.[93] Left ventricular function is normal when hearts from these animals are retrogradely perfused.[93] However, the cardiac-specific GLUT4 knockout may have increased susceptibility to ischemia, highlighting the importance of GLUT4-mediated glucose uptake and glycolysis in the ischemic heart.

CONCLUSION

Tremendous advances have recently been achieved in our understanding of the cellular and molecular mechanisms regulating glucose transport in the heart and other tissues. An intricate network of signaling molecules and intracellular proteins trigger and mediate the vesicular movement of GLUT vesicles, targeting them to the sarcolemma. Ongoing research in this area promises to further define these mechanisms in the heart, which may lead to potential targets for pharmacologic or gene therapy to modulate glucose transport in the heart.

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