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Alterations in Glucose Transporter Expression and Function in Diabetes: Mechanisms for Insulin Resistance

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Abstract Insulin resistance is a major pathologic feature of human obesity and diabetes. Understanding the fundamental mechanisms underlying this insulin resistance has been advanced by the recent cloning of the genes encoding a family of facilitated diffusion glucose transporters which are expressed in characteristic patterns in mammalian tissues. Two of these transporters, GLUT1 and GLUT4, are present in muscle and adipose cells, tissues in which glucose transport is markedly stimulated by insulin. To understand the mechanisms underlying in vivo insulin resistance, regulation of these transporters is being investigated. Studies reveal divergent changes in the expression of GLUT1 and GLUT4 in a single cell type as well as tissue specific regulation. Importantly, alterations in glucose transport in rodent models of diabetes and in human obesity and diabetes cannot be entirely explained by changes in glucose transporter expression. This suggests that defects in glucose transporter function such as impaired translocation, fusion with the plasma membrane, or activation probably contribute importantly to in vivo insulin resistance.

Key words: glucose transport, insulin action, Type II diabetes (NIDDM), hexose transporter, translocation

Recent molecular cloning studies reveal that the transport of glucose across the plasma membrane of mammalian cells is mediated by a family of facilitated diffusion glucose transporters. These structurally related proteins are products of homologous but distinct genes with different tissue distributions (Table I) [for review see 1,2]. Salient to the field of insulin action is the fact that one of these glucose transporters, GLUT4, is expressed almost exclusively in tissues in which glucose transport is rapidly and markedly stimulated by insulin—that is, muscle and adipose cells. GLUT1 is also expressed in these highly insulin responsive tissues as well as in many "non-insulin responsive" tissues.

To understand the cellular and molecular mechanisms underlying insulin resistance, investigations have focused on the level of expression of these transporters. Most studies have been carried out in adipose cells which have been considered to be a model for skeletal muscle, a much more difficult tissue to investigate. However, recently we have shown striking tissue specific regulation of glucose transporters in muscle and adipose cells [3,4]. Furthermore, alterations in the level of expression of transporter genes do not always explain changes in glucose transport. Changes in mRNA levels may not correspond to changes in the level of the protein due to post-transcriptional regulation of transporters. Importantly, the insulin resistant glucose transport characteristic of states such as diabetes, obesity, and fasting appears to result, at least in part, from alterations in functional aspects of glucose transporters [3–5]. In diabetes, sequential defects may occur which affect both transporter function and expression.

MECHANISMS BY WHICH INSULIN STIMULATES GLUCOSE TRANSPORT

More than ten years ago the translocation hypothesis was proposed to describe the mechanism by which insulin stimulates glucose transport in adipose cells and muscle (Fig. 1) [6]. Insulin, binding to its receptor, generates a series of signals resulting in the translocation of transporters from an intracellular pool associated with specific membrane vesicles to the plasma membrane where they fuse and promote glucose entry into the cells. In states in which

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TABLE I. Facilitated Diffusion Glucose Transporters in Mammalian Tissues

Gene	Nomenclature	Major sites of expression
GLUT1	Erythrocyte	Many tissues; high levels in human erythrocytes, brain, blood brain barrier, placenta, kidney, colon
GLUT2	Liver	Liver, pancreatic β cells, kidney, small intestine
GLUT3	Brain	Many tissues; high levels in brain, placenta, kidney
GLUT4	Muscle/fat	Skeletal muscle, heart, white adipose cells, brown fat
GLUT5	Small intestine	Small intestine, kidney
GLUT6	Pseudogene	

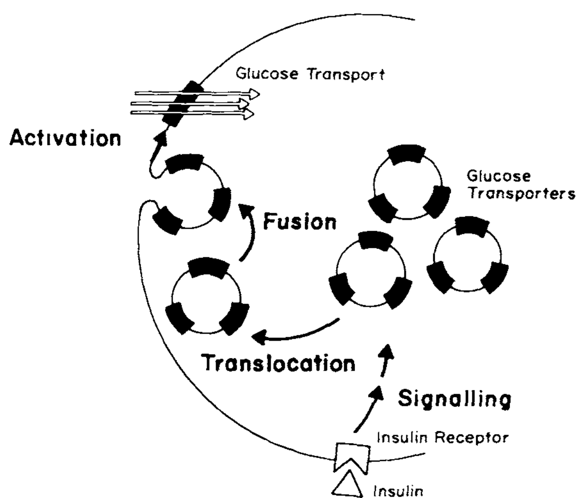

Fig. 1. Hypothetical model of the steps involved in insulin stimulated glucose transport. Curved line represents the plasma membrane of a muscle or adipose cell. Transporter proteins are depicted associated with specific membrane vesicles.

insulin action is altered in peripheral tissues, the abundance of glucose transporters in the intracellular pool may be altered, affecting the number translocated to the plasma membrane in response to insulin. More recently it has become apparent that changes in the activity of transporters may also contribute to insulin resistant or hyperresponsive glucose transport [5,7]. This *Prospect* will discuss how specific physiological factors may regulate glucose transporter expression and activity and highlight key questions which need to be answered to understand these mechanisms.

ALTERATIONS IN GLUCOSE TRANSPORT IN ADIPOSE CELLS: DIABETIC RAT MODELS

Effects on Glucose Transporter Expression

In isolated adipose cells from 7 day streptozotocin diabetic rats, 3-0-methylglucose transport in the basal state is unaltered while insulin stimulated glucose transport decreases ~60% [8]. With 7 days of insulin treatment, basal glucose transport is still minimally altered but insulin stimulated transport is not only restored but actually increases to threefold control levels [8]. Immunoblotting of adipose cell subcellular membrane fractions from these rats reveals differential regulation of GLUT1 and GLUT4. In control rats, in plasma membranes from adipose cells in the basal state there are very few GLUT4 transporters and after insulin stimulation, levels increase ten- to twentyfold. In adipose cell plasma membranes from diabetic rats GLUT4 is markedly decreased even in the insulin stimulated state. In chronically insulin treated diabetic rats, GLUT4 levels in plasma membranes from insulin stimulated cells are not only restored but increased above control [8]. Most of GLUT4 transporters in adipose cells are sequestered in a large intracellular pool associated with low density microsomes; ~50% disappear from this pool in response to insulin. In untreated diabetic rats, this intracellular pool is reduced and in insulin treated diabetic rats the pool is restored [8].

Unlike GLUT4, GLUT1 is present in similar amounts in plasma membranes and low density microsomes in the basal state and undergoes a two- to threefold translocation in response to insulin [8]. It is much less abundant in adipose cells than GLUT4 [9,10]. Levels of the GLUT1 protein are unaffected by diabetes or insulin treatment in spite of the fact that insulin treatment increases GLUT1 mRNA to threefold control levels [8]. This is one of many examples of post-transcriptional regulation of glucose transporters in vivo [7]. In addition, these studies illustrate that two glucose transporter isoforms in a single cell type can be divergently regulated in association with metabolic perturbations. These observations suggest that the insulin resistant glucose transport in adipose cells from diabetic rats may be due to a decreased intracellular pool of GLUT4 with fewer available to be translocated to the plasma membrane in re-

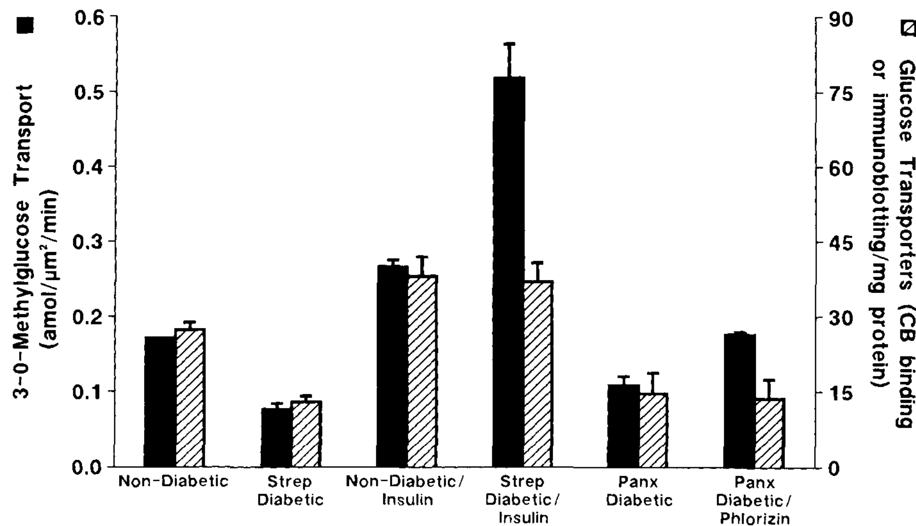

Fig. 2. Comparison of insulin stimulated glucose transport activity in intact adipose cells and glucose transporters in plasma membranes from the same cells in rat models of diabetes and treatment with insulin or phlorizin. Panx, 90% pancreatectomy; Strep, streptozotocin. Reproduced from [5] with permission of the American Society for Clinical Investigation.

sponse to insulin. With chronic insulin treatment GLUT4 transporters are restored in the intracellular pool and in the plasma membranes. However, the increase in transport activity is much greater than the increase in transporter number, suggesting that insulin treatment of the diabetic rat also increases transporter intrinsic activity (Fig. 2) [8].

Effects on Glucose Transporter Activity

To understand the pathogenesis of states such as diabetes it is important to determine the effects of ambient glucose levels independent of insulin on glucose transporter regulation. For example, is there a "glucose toxicity" effect? Our previous studies had shown that hyperinsulinemia induced by insulin infusion in normal rats resulted in an increased intracellular pool of glucose transporters with more translocated to the plasma membrane in response to insulin [11]. This correlated with an increase in insulin stimulated glucose transport in the intact cell (Fig. 2).

To study the effects of glucose independent of insulin we used a milder form of diabetes produced by 90% pancreatectomy. Euglycemia was restored with phlorizin which impairs renal tubular reabsorption of glucose enhancing glucose excretion. Thus, phlorizin treatment normalizes blood glucose in diabetic rats without increasing insulin secretion. Basal glucose transport in adipose cells of pancreatectomized diabetic rats before or after phlorizin treatment was minimally altered. In contrast, insulin stimulated glucose transport decreased ~45% in diabetic rats and was fully restored with phlorizin treatment. Thus, restoration of euglycemia even without insulin therapy restored insulin responsiveness at the cellular level.

With diabetes, GLUT4 levels in plasma membranes from adipose cells acutely stimulated with insulin were reduced ~50% compared to control. Importantly, with phlorizin treatment, GLUT4 levels remained reduced at diabetic levels (Fig. 2). In the intracellular pool GLUT4 levels were also reduced 50% in diabetic rats and remained reduced in phlorizin treated rats [5]. This effect appeared to be pretranslational since GLUT4 mRNA levels in adipose cells were also reduced with diabetes and with phlorizin treatment. This was in direct contrast to the effect of insulin treatment which increases GLUT4 mRNA levels [8]. With phlorizin treatment the same number of transporters as in the diabetic state were transporting more glucose (Fig. 2), indicating that modulation of ambient glucose levels appears to alter the intrinsic activity of transporters. Previous in vitro and in vivo evidence for intrinsic activity changes has been reviewed [6,7,12].

REGULATION OF GLUCOSE TRANSPORTERS IN SKELETAL MUSCLE

Skeletal muscle, not adipose cells, is the major tissue responsible for insulin mediated glucose uptake in vivo [13]. Although studies of glucose

transport, as well as subcellular fractionation, are much more difficult in muscle, such studies are necessary to understand the cellular and molecular mechanisms underlying insulin resistance.

Localization of Glucose Transporter Isoforms in Muscle

In contrast to adipose cells, in muscle GLUT1 and GLUT4 appear to be expressed in different cell types. Immunofluorescence studies show that GLUT1 is primarily in the perineurial sheath, whereas GLUT4 is within the muscle fiber [4,14]. Recent electron micrographic studies using immunogold labelling of GLUT4 demonstrate its presence within muscle fibers as well as its insulin stimulated translocation from a tubulo-vesicular fraction to the plasma membrane [15]. Hence it appears that in muscle, as in adipose cells, GLUT4 is more important than GLUT1 in mediating insulin stimulated glucose transport.

Tissue Specific Regulation of GLUT4

Diabetic rodent models. Reports of insulin stimulated glucose uptake in isolated muscle from diabetic rodents show conflicting results. In isolated hindlimb muscles from streptozotocin diabetic and spontaneously diabetic rodents, maximal insulin stimulated glucose transport was decreased [16–18] or normal [19,20] and the sensitivity to insulin was increased [19]. Perfused hindlimb studies in diabetic rats failed to show insulin resistant glucose uptake [21] except in the presence of ketosis [22]. Even in studies demonstrating diminished insulin stimulated glucose transport in muscle of diabetic rats, the defect was reversed with incubation of the isolated muscle in Krebs-Henseleit bicarbonate buffer [16], suggesting that circulating factors in vivo may inhibit glucose uptake in muscle.

Studies in streptozotocin diabetic rats before and after insulin treatment demonstrate marked tissue specific regulation of GLUT4 in muscle and adipose cells (Fig. 3). With 7 days of diabetes, GLUT4 protein levels in muscle are similar to control while GLUT4 decreases 90% in adipose cells [4]. After 14 days of diabetes when animals are catabolic and volume depleted, GLUT4 decreases in muscle. Other studies [23] show a decrease in the GLUT4 protein earlier and the difference in timing probably reflects differences in metabolic characteristics of the rats. The decrease in GLUT4 is partially prevented by 3 days of insulin therapy and completely prevented by 5 and 7 days of insulin, so at 7 days the level of GLUT4 in muscle remains at diabetic levels, whereas the level of GLUT4 in fat is markedly increased from diabetic levels (Fig. 3). Importantly, in our studies at 7 days of diabetes there is striking in vivo insulin resistant glucose transport in muscle which cannot be explained by a decrease in GLUT4 or GLUT1 transporters [4]. Thus, for studies of glucose transporter regulation, adipose cells are not necessarily a good model for muscle due to tissue specific regulation. Furthermore, sequential defects appear to contribute to the insulin resis-

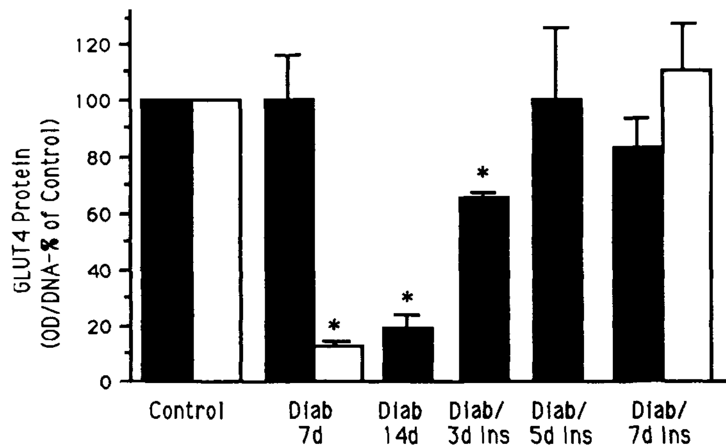

Fig. 3. Tissue specific regulation of GLUT4 in skeletal muscle (■) and adipose cells (□) of diabetic (Diab) rats before and after insulin (Ins) treatment. Muscle was a mixture of red and white gastrocnemius and soleus. GLUT4 was detected by immunoblotting with an anti-peptide antiserum and bands were quantitated by scanning densitometry. Reproduced from [4] with permission of the American Society for Clinical Investigation.

tant glucose transport in muscle in diabetic rats and the impaired insulin stimulated transport in vivo precedes any fall in GLUT4 protein levels.

Fasting as a model of insulin resistance. The phenomenon of in vivo factors antagonizing the activity of glucose transporters is even more dramatically evident in the fasting model of insulin resistance. Fasting in rats [24] and humans [25] is characterized by profound in vivo insulin resistant glucose uptake in muscle. Recently we reported increased expression of GLUT1 and GLUT4 at the mRNA and protein levels in hindlimb muscle of fasted rats [3]. This is in agreement with previous studies showing no decrease [22,26] or even an increase [19] in insulin stimulated glucose uptake in isolated soleus muscle and perfused hindlimb from fasted rats. Our investigations are now focusing on determining whether the translocation of transporters is impaired or their intrinsic activity is altered to cause the in vivo insulin resistant glucose uptake characteristic of fasting.

Hyperinsulinemic, insulin resistant rodent models. Functional defects in GLUT4 appear to be important not only in the insulinopenic states of streptozotocin diabetes and fasting but also in models of insulin resistant glucose uptake which display metabolic characteristics more similar to human obesity and Type II diabetes. For example in the Zucker fa/fa rat, a model of genetic obesity with endogenous hyperinsulinemia and insulin resistant glucose uptake in vivo, various studies point to a transport defect in muscle [27,28]. Studies show no change in GLUT1 or GLUT4 mRNA or protein levels in muscle of obese Zucker rats compared to lean littermates [29–31]. Even when obese rats are made acutely diabetic with streptozotocin, there is still no change in GLUT1 or GLUT4 mRNA or protein levels in skeletal muscle [31]. This is in marked contrast to dramatic changes in GLUT4 levels in adipose cells from these rats [29,31]. Similarly, in hyperinsulinemic, obese, diabetic db/db mice, GLUT4 expression in skeletal muscle is unaltered from lean levels [32]. Thus, in insulin resistant states, regardless of whether ambient insulin levels are low or high, insulin resistance can not be explained by changes in GLUT4 expression in skeletal muscle. These findings again suggest a probable defect in glucose transporter function. A recent abstract [33] indicates that in muscle of obese Zucker rats, the translocation of transporters is deranged and this may be the major mechanism for insulin resistant glucose uptake in this model.

HUMAN STUDIES

GLUT4 expression has been investigated in adipose cells and skeletal muscle from obese and diabetic humans. Two studies in adipose cells disagree as to whether GLUT4 expression decreases with obesity but agree that it is depressed with Type II diabetes [34,35]. In fact, the pretranslational suppression appears to be present even in subjects with impaired glucose tolerance [34]. In contrast, several studies agree that GLUT4 expression in vastus lateralis muscle of subjects with Type II diabetes is similar to that in weight-matched non-diabetic controls regardless of degree of metabolic control, duration of diabetes, or mode of antidiabetic therapy [36–39].

Most studies also show no effect of human obesity on GLUT4 expression in skeletal muscle [36,39]. The one study [38] which reports an ~20% decrease with morbid obesity finds the decrease only in abdominal rectus and not in vastus lateralis muscle. The effect is much smaller than the decrease in insulin stimulated glucose uptake in vivo or in muscle strips in vitro [40] from these subjects. Even in Type I diabetics who share some characteristics with the streptozotocin rat model, GLUT4 levels are unaltered in skeletal muscle and do not correlate with important physiological factors [39]. So in human obesity and diabetes, as in rat models, there is tissue specific regulation of glucose transporters and changes in transporter expression do not explain in vivo insulin resistant glucose uptake.

However, all human studies to date have been cross-sectional and have revealed a considerable range of values for glucose transporter levels even among lean controls [34–41]. There are many potential determinants of GLUT4 levels in muscle including fiber type which has been shown to be important in rodents [42]. Hence longitudinal studies are needed to determine whether in individual subjects GLUT4 levels can be modulated by therapeutic interventions such as weight reduction, improvement in glycemic control, reduction in dietary fat content, or exercise. Exercise training is particularly promising since it increases GLUT4 levels in normal [43] as well as obese Zucker [30] rats.

FUTURE DIRECTIONS

The observations discussed above suggest that several mechanisms may be important in the pathogenesis of insulin resistant glucose uptake in peripheral tissues. Although the expression of GLUT4 is markedly altered in adipose cells in both insulinopenic and hyperinsulinemic insulin resistant states, expression in muscle is often unchanged. These data generate a number of exciting questions. Understanding the basis for this tissue specific regulation will require identification of regulatory sequences of the transporter genes which will permit identification, purification, and quantitation of tissue specific regulatory factors. An adipocyte differentiation dependent nuclear transcription factor has been identified in 3T3-L1 adipocytes and has been shown to trans-activitate the GLUT4 promoter [44]. However, its physiological significance is unclear. Post-translational regulation of transporter expression also appears important and the mechanisms underlying this regulation need to be delineated.

Potentially additional glucose transporter isoforms may be present in muscle and adipose cells. Both GLUT3 and GLUT5 mRNA are expressed at relatively low levels in human adipose and muscle tissue [1]. Studies need to determine whether this expression is in adipose or muscle cells or in the surrounding connective tissue elements and whether the corresponding transporter proteins are present in significant amounts. However, even if other isoforms are present in muscle and fat, GLUT4 is likely to be of major importance due to its specific distribution in these tissues and its marked translocation to the plasma membrane in response to insulin.

Thus, studies in skeletal muscle now need to focus on whether there are changes in the subcellular distribution of GLUT4 or in functional processes including translocation in response to insulin, fusion with the plasma membrane and exposure to the extracellular milieu, affinity for glucose a K_m change, or intrinsic activity, a V_{max} effect (Fig. 4). The biochemical nature of such functional defects is of great interest. Initial attempts to define "intrinsic activity" changes have not detected biochemical alterations in the transporter. However, these functional defects may be due to factors extrinsic to the transporter such as alterations in the vesicles with which they are associated or in elements of the cytoskeleton. Of key importance will be studies investigating potential changes in intracellular signaling pathways resulting in alterations in transporter translocation and/or intrinsic activity. Evidence is accumulating for the role of small GTP binding proteins in vesicle fusion [45] and one study suggests that GTP binding proteins may play an important role in GLUT4 translocation [46]. Thus, investigations also need to identify specific G proteins involved in the movement and fusion of GLUT4 containing vesicles. Such information will lead to a deeper understanding of the pathogenesis of insulin resistance and will potentially open new therapeutic avenues for human diabetes.

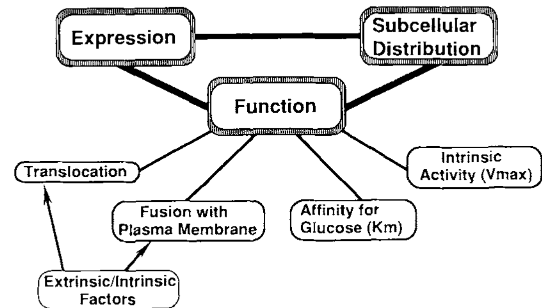

Fig. 4. Conceptualization of the potential alterations in glucose transporters which may contribute to changes in insulin responsive glucose transport in vivo.

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