

Diabetes, Glucose Transport and Hypoglycaemic Agents

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Abstract – Diabetes mellitus is a complex metabolic derangement with hyperglycaemia being the most characteristic symptom of diabetes. Hyperglycaemia can be caused by an increase in the rate of glucose production by the liver or by a decrease in the rate of glucose use by peripheral tissues. Impaired glucose transport is one of the major factors contributing to insulin resistance in type 2 diabetic patients. The ability of insulin to mediate tissue glucose uptake is a critical step in maintaining glucose homeostasis and in clearing the post-prandial glucose load. Glucose transport is mediated by specific carriers called glucose transporters (GLUTs). In this article, the functional importance and molecular mechanisms of insulin-induced glucose transport and development of hypoglycaemic agents which increase glucose transport are reviewed.

Keywords □ diabetes, glucose transport, hypoglycemic agent, insulin, phosphatidylinositol 3-kinase, TC10

Diabetes mellitus is a complex metabolic derangement and is classified as type 1 and type 2 diabetes (World Health Organization Study Group, 1985). Type 1 diabetes, also called insulin-dependent diabetes mellitus, usually develops in children and adolescents, but can also develop in adults (Yoon and Jun, 1998). Type 1 diabetes is characterized by the absolute insulin deficiency caused by the destruction of pancreatic β -cells by a complicated and chronic pathogenic process of islet-specific autoimmune reaction (Yoon and Jun, 2001).

Type 2 diabetes, non-insulin-dependent diabetes mellitus, accounts for over 85% of the diabetic population and appears during the later decades of life (DeFronzo, 1988), except the maturity onset diabetes of the young (MODY) (Pirart, 1978). Genetic factors (e.g., genes involved in insulin resistance, obesity genes, and genes involved in β -cell function) and environmental factors (e.g., physical activity and diet) play a strong role in the development of the disease. In most genetically predisposed individuals, there is a slow progression from a normal state to insulin resistance, followed by hyperinsulinemia, glucose desensitization, defects in insulin secretion, impaired glucose tolerance, and then to hyperglycaemia (Jun *et al.*, 1999).

The characteristic symptoms of diabetes are polyuria, increasing thirst and appetite, tiredness, weight loss and hyperglycaemia. Hyperglycaemia, the most characteristic symptom of

diabetes is defined as fasting blood glucose levels above 250 mg/dl (Rifkin and Porte, 1997).

Diabetic patients are subject to numerous secondary complications such as microvascular, macrovascular, and neuropathic diseases, which greatly influence the lives of patients (Fajans and Conn, 1965). The development of complications in the diabetic patient relates largely to the severity and chronicity of hyperglycaemia. Thus, regulation of blood glucose is the major target for the management of type 2 diabetes, which can prevent the development of complications and improve the quality of life (UK Prospective Diabetes Study Group, 1998).

GLUCOSE TRANSPORT SYSTEM

Glucose uptake by tissues plays an essential role in glucose homeostasis. The liver takes up approximately one-third of an oral glucose load, the muscle and adipose tissue take up one-third, and non-insulin-dependent tissues take up the remaining third (Pagliassotti and Horton, 1994; Meyer *et al.*, 2002; Moore *et al.*, 2003). Hyperglycaemia can be caused by the increased glucose production by the liver or decreased glucose disposal by peripheral tissues (Guyton and Hall, 1996). Glucose transport is the first step for glucose utilization in peripheral tissues, and impaired glucose transport in adipose tissue and muscle is one of the major factors contributing to insulin resistance in diabetic patients (James and Piper, 1994). The ability of insulin to mediate tissue glucose uptake is a critical step in maintaining glucose homeostasis and in clear-

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ing the post-prandial glucose load (DeFronzo *et al.*, 1985; Kruszynska and Olefsky, 1996). Patients with type 2 diabetes exhibit a marked reduction in insulin-mediated glucose disposal (Ginsberg, 1975; Reaven, 1983). Thus, increasing glucose transport in the muscle and adipose tissue results in the decrease of blood glucose levels, contributing to the control of hyperglycaemia.

Glucose transport is mediated by specific facilitative carriers called glucose transporters (GLUTs) which do not require ATP for their function (Baldwin, 1993). Currently, 13 GLUT genes have been identified and functional GLUTs are listed in Table 1. These proteins exhibit a high degree of sequence homology but vary in their kinetic characteristics, sensitivity to hormonal and environmental stimuli, as well as tissue and subcellular distributions (Ducluzeau *et al.*, 2002).

GLUT1 is widely distributed throughout the tissues and especially abundant in red blood cells, endothelial cells and tissue culture cell lines. Their major function is to facilitate basal glucose uptake in many types of cells. It mediates glucose transport in growing cells and across the blood-brain barrier. GLUT2 is a part of glucose sensing system in pancreatic β -cell and its expression is limited to pancreatic β -cell, hepatocyte, intestine, and kidney. GLUT4 is largely expressed in insulin-responsive tissues, such as skeletal and cardiac muscle, and adipocytes. It is known that 90% of glucose transporters in these tissues are GLUT4, demonstrating its pivotal role in insulin-sensitive glucose uptake, and in postprandial glucose disposal.

INSULIN-INDUCED GLUCOSE TRANSPORT

Insulin stimulates various glucose metabolisms including glucose transport in insulin responsive tissues such as liver, muscle and adipose tissue. Insulin-stimulated glucose transport is mediated by insulin-responsive glucose transporter, GLUT4 which is mainly expressed in muscle and adipose tissue (Baldwin, 1993). Without insulin stimulation, more than 95% of the GLUT4 is located in GLUT4 storage vesicles (GSV) and the trans-Golgi network (TGN) vesicles close to the plasma membrane in the cytoplasm of adipocytes or muscle (Simpson *et al.*, 2001). GLUT4-containing vesicles are almost entirely sequestered within the cell and sorted from the constitutive recycling pathway into a compartment that has a very slow exocytic rate (Czech and Corvera, 1999) (Fig. 1).

Upon insulin stimulation, there is a rapid and marked increase in the amount of GLUT4 at the cell surface and glucose transport. Insulin increases exocytosis of GLUT4-containing vesicles more than 5 fold while the rate of endocytosis from the cell surface decreased by 2-fold (Millar *et al.*, 1999) (Fig. 2). Insulin increases constitutive recycling and efflux of GLUT4 in TGN vesicles as well as exocytosis of GLUT4 in GSVs from early endosomes (Tanner and Lienhard, 1987). The major population of GLUT4 translocated by insulin is originated from GSVs because the effect of insulin on the exocytosis of GSV in early endosomes is much greater than that on TGN vesicles (Rea and James, 1997).

The docking and fusion of GLUT4 vesicles, which are activated by insulin signal pathway, are mediated by distinct machinery at the cell surface (Martin *et al.*, 2000). v-Soluble N-Ethylmaleimide attachment protein receptor (SNARE) and t-SNARE are required for the translocation of GLUT4. The v-

Table 1. The mammalian facilitative glucose transporter family

Isoform	Tissue Distribution	Proposed Function
SGLT1	Kidney, intestine	Na ⁺ dependent active transport.
GLUT1	Ubiquitous; abundant in human erythrocytes, placenta and fetal tissues, brain, endothelia, and many immortalized cell lines.	Basal and growth factor-stimulated transport. Blood-tissue barrier transport.
GLUT2	Liver, kidney, pancreatic β -cell, small intestine	Low affinity transporter. Hepatic glucose output. Part of the glucose sensor in islets and liver. Transepithelial transport in kidney and gut.
GLUT3	Neurons, placenta	High-affinity transporter. Unabated transport into central nervous system.
GLUT4	Skeletal and cardiac muscle, brown and white adipose tissue	Insulin-stimulated glucose transport.
GLUT5	Small intestine, spermatozoa, smaller amounts in adipose tissue, muscle, brain and kidney	High-affinity fructose transporter.
GLUT7	Liver	Mediates glucose release from endoplasmic reticulum coupled to glucose-6-phosphatase.

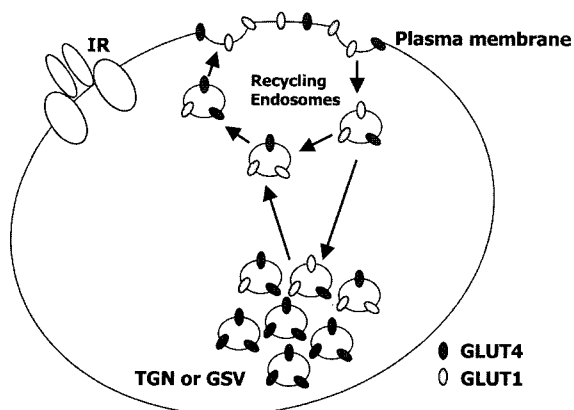


Fig. 1. Regulation of GLUT4 Translocation in Basal (resting) State. In basal or non-stimulated state, more than 95% of the GLUT4 is located in GLUT-4 storage vesicles (GSV) and the trans-Golgi network (TGN) vesicles. In this state, GLUT4-containing vesicles are almost entirely sequestered within the cell and sorted from the constitutive recycling pathway into a compartment that has a very slow exocytic rate.

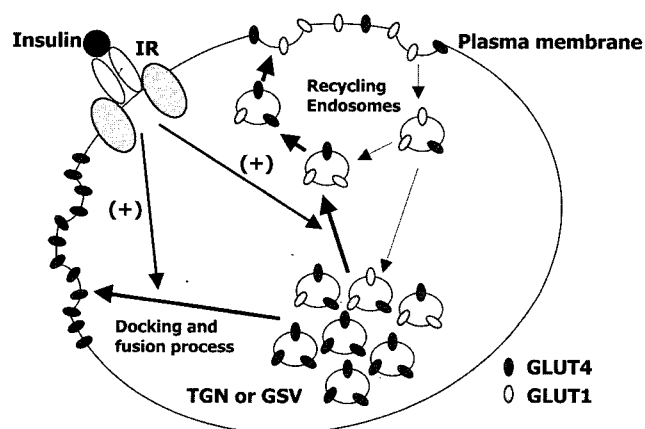


Fig. 2. Regulation of GLUT4 Translocation in Insulin-stimulated State. Insulin causes a rapid and marked increase in the amount of GLUT4 at the cell surface by increasing exocytosis of GLUT4-containing vesicles more than 5 fold, while decreasing the rate of endocytosis of them from the cell surface by 2-fold. The major population of GLUT4 translocated by insulin is originated from GSVs rather than TGN vesicles.

SNARE vesicle associated membrane protein2 (VAMP2) has been localized to a subpopulation of intracellular GLUT4 vesicles, lending morphological support to the existence of GSVs (Randhawa *et al.*, 2000; Millar *et al.*, 1999). VAMP2 function is required for insulin-stimulated GLUT4 translocation. Syntaxin 4 and SNARE associated protein-23 (SNAP-23) are t-SNAREs that form stable complexes with VAMP2, which localize to the plasma membrane and have been implicated in insulin action (Rea *et al.*, 1998).

SIGNAL TRANSDUCTION PATHWAYS RELATED TO GLUCOSE TRANSPORT

Phosphatidylinositol 3-kinase pathway

Binding of insulin on insulin receptor changes the conformation of receptor α -subunit, which in turn activates tyrosine kinases activity of receptor β -subunit and induces the phosphorylation of insulin receptor substrate (IRS) family members (Lane *et al.*, 1990). The phosphorylated IRS proteins recruit the phosphatidylinositol 3-kinase (PI3-K) by its association with the regulatory subunit of PI3-K (p85 α) (Shepherd *et al.*, 1998). PI3-K generates the lipid mediator of insulin, phosphatidylinositol-3,4,5,-triphosphate (PIP₃) (Jiang *et al.*, 1998). Blockade of insulin-induced PIP₃ generation with PI3-K inhibitors or with a dominant negative PI3-K mutant results in complete inhibition of insulin-induced glucose transport and GLUT4 translocation in adipocytes (Kotani *et al.*, 1995). This demonstrates the absolute requirement of PI3-K in insulin-induced translocation of GLUT4 from both the endosomal and GSV pools.

PIP₃ recruits serine/threonine kinase Akt/protein kinase B (PKB) to the plasma membrane where 3'-phosphoinositide-dependent kinase 1 (PDK1) activates Akt/PKB by phosphorylating critical threonine residues in its activation loops (Hill *et al.*, 1999; Alessi *et al.*, 1997). PDK1 activation by PIP₃ is also involved in the activation of atypical protein kinase Cs (PKC ζ) by insulin (Standaert *et al.*, 2001; Arribas *et al.*, 2003). Recent findings suggest that atypical PKCs and Akt/PKB serve as important positive regulators of insulin-stimulated glucose metabolism, and active forms of these two enzymes appear to be required for insulin-induced GLUT4 translocation to plasma membrane (Simpson *et al.*, 2001).

TC10 Pathway

A recent series of experiments have revealed the PI3-K-independent glucose transport mechanism. The plasma membrane of adipocytes is characterized by the presence of multiple caveolar, large vesicular invagination of plasma membrane (Ribon and Saltiel, 1997; Ribon *et al.*, 1998). Caveolar appears to play an important role in insulin-induced tyrosine phosphorylation of c-Cbl by insulin receptor (Ribon *et al.*, 1998; Mastick *et al.*, 1995). Phosphorylated c-Cbl is recruited to lipid rafts as a complex with CAP (Cbl associated protein), which binds to flotillin (Baumann *et al.*, 2000). CAP may aid c-Cbl phosphorylation by insulin receptors and recruitment (Ahmed *et al.*, 2000).

TC10 is one of the Rho family GTPases expressed in muscle and adipose tissue, which is associated with lipid raft. Phospho-

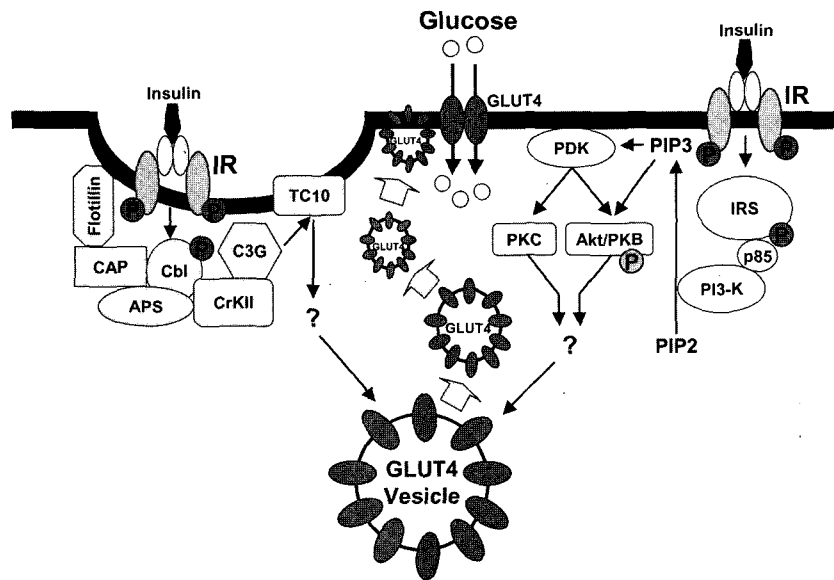


Fig. 3. Signal transduction pathways related to insulin-induced GLUT4 translocation. Recruitment of PI3-K by phosphorylated IRS results in the production of PIP3 which in turn activates PDK1 and Akt/PKB. Phosphorylated Cbl induces complex formation of Cbl-CAP-CrkII-C3G in lipid raft. C3G functions as a guanine nucleotide exchange factor for TC10. These two pathways play the role to elicit GLUT4 translocation through membrane trafficking system. IR: insulin receptor; IRS, insulin receptor substrate; PDK, 3'-phosphoinositide-dependent kinase; PI3-K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PIP3, phosphatidylinositol 3,4,5-triphosphate.

rylated c-Cbl recruits C3G, which is a guanynucleotide exchange factor of TC10, via an SH3 domain-containing adaptor, CrkII. Thus the insulin-induced localization of the CAP/Cbl/CrkII/C3G complex promotes the conversion of GDP-bound TC10 to an active GTP-bound state (Chiang *et al.*, 2001). While the molecular target of TC10 is currently unknown, TC10 activation may be required for insulin-stimulated GLUT4 translocation from the GSV pool, with no apparent effect on GLUT4 in the endosomal pool (Watson *et al.*, 2001).

APS (adaptor protein with Pleckstrin homology and Src homology 2 domains) is recruited by the insulin receptor and is essential for GLUT4 translocation. Recently the primary and essential role of APS for recruitment of c-Cbl and CAP in insulin signaling was reported. In the absence of APS, there is no association of insulin receptor and CAP, and no phosphorylation of Cbl by insulin receptor (Ahn *et al.*, 2004).

Hypoglycaemic agents

Oral hyperglycaemic agents are used to compensate insulin and manage metabolic abnormalities associated with hyperglycaemia in diabetic patients (Moller, 2001; Inzucchi, 2002). The studies of overexpression or ablation of GLUT4 in skeletal muscle and adipose tissue revealed that glucose transport is the rate limiting step for glucose disposal, and the absence of GLUT4 results in impaired insulin tolerance and defects in glu-

ucose metabolisms (Wallberg-Henriksson and Zierath, 2001; Carvalho *et al.*, 2004). Thus GLUT4 is an attractive target for the development of hypoglycaemic agents.

Hypoglycaemic agents are known to increase glucose transport. Sulfonylureas increase insulin secretion, proinsulin biosynthesis, but decrease glucagon secretion (Zimmerman, 1997). Sulfonylureas also have effects on peripheral insulin resistance such as decreased glucose transport in diabetic individuals (Farese *et al.*, 1991). Metformin decreases hepatic glucose production, increases glucose uptake by muscle and adipose tissue, and alters intestinal function (Hundal *et al.*, 2000; Bailey and Turner, 1996). However, these hypoglycaemic agents mainly elicit their effect through insulin secretion or inhibition of hepatic glucose output rather than glucose transport (Inzucchi, 2002).

The materials which increases glucose transport and GLUT4 translocation through insulin signalling-dependent or independent pathway are intensively examined for the treatment of diabetes. Natural products such as ginseng (Attele *et al.*, 2002), green tea (Wu *et al.*, 2004; Tsuneki *et al.*, 2004) and flavonoids (Khil *et al.*, 1997; Khil *et al.*, 1999; Choi *et al.*, 2004) are examined for their effect on glucose transport and hypoglycaemic effects in diabetic animal models. Synthetic small molecules or chemicals are also tested for potential pharmacological uses as insulin mimetics or stimulatory agent for glucose transport (Ciaraldi *et al.*, 1995; Sarges *et al.*, 1996; Zhang *et al.*, 1999;

Strowski *et al.*, 2004).

Newly introduced thiazolidinediones, which are known as insulin sensitizers, increase peripheral glucose disposal via glucose transport and GLUT4 translocation (Ciaraldi *et al.*, 1995; Shintani *et al.*, 2001; Ciaraldi *et al.*, 2002) by activating peroxisome proliferators-activated receptor- γ (PPAR- γ). PPAR- γ is very important for the expression of molecules such as GLUT1, GLUT4, and p85 PI3-K that play a critical role in insulin action (Mudaliar and Henry, 2001). It is also reported that rosiglitazone normalizes cellubrevin, VAMP-2 and syntaxin 4 resulting in the reversion of elevated v- and t-SNARE in insulin resistance state (Maier *et al.*, 2000).

CONCLUSION

Insulin is responsible for lowering blood glucose by increasing glucose transport and glucose utilization in its major target tissues such as liver, muscle and adipose tissue. The regulation of blood glucose is the major target for the management of type 2 diabetes. However, in type 2 diabetic patients, insulin resistance prevents insulin from decreasing blood glucose because of less- or non-responsiveness of peripheral tissues to insulin. Therefore impaired glucose transport is considered as one of the pathogenesis of insulin resistance. For these reasons, increasing glucose transport by any means in the muscle and adipose tissue results in the decrease of blood glucose levels, contributing to the control of hyperglycaemia.

Translocation of GLUT4 to the cell surface is impaired in insulin resistant muscle and adipose tissue because the overall levels of GLUT4 are normal in patients with type 2 diabetes (Kahn, 1992). Furthermore, the overexpression of GLUT4 in either adipose tissue or muscle in animals exhibit a marked improvement in whole body insulin sensitivity implying that this may be a possible approach for attaining successful management of type 2 diabetes (Liu *et al.*, 1993; Tozzo *et al.*, 1993). Thus potentiation of glucose transport by increasing GLUT4 translocation to the cell surface through the stimulation of insulin signal transduction pathways or activation of gene expression of GLUT4, especially in skeletal muscle, would have enormous therapeutic benefit for type 2 diabetes management.

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