Review Articles

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., *Editor*

GLUCOSE TRANSPORTERS AND INSULIN ACTION

Implications for Insulin Resistance and Diabetes Mellitus

PETER R. SHEPHERD, PH.D., AND BARBARA B. KAHN, M.D.

INSULIN was discovered more than 75 years ago, but only recently have we begun to understand the mechanisms by which insulin promotes the uptake of glucose into cells. This review discusses recent advances, their contribution to our understanding of the pathogenesis of diabetes mellitus, and their implications for the design of new therapies to prevent and treat diabetes and its complications.

ROLE OF GLUCOSE TRANSPORTERS IN MAINTAINING GLUCOSE HOMEOSTASIS

Carbohydrates, and glucose in particular, are an important source of energy for most living organisms. Tissues such as the brain need glucose constantly, and low blood concentrations of glucose can cause seizures, loss of consciousness, and death. However, prolonged elevation of blood glucose concentrations, as in poorly controlled diabetes, can result in blindness, renal failure, cardiac and peripheral vascular disease, and neuropathy. Therefore, blood glucose concentrations need to be maintained within narrow limits. This is accomplished by the finely tuned hormonal regulation of peripheral glucose uptake and hepatic glucose production. During fasting, most of the glucose in the blood is supplied by the liver and is used by the brain, independently of insulin. After a meal, the rise in blood glucose levels rapidly stimulates insulin secretion, which results within minutes in increased glucose transport, metabolism, and storage by muscle and adipocytes. In addition, insulin both inhibits glucagon secretion and lowers serum free-fatty-acid concentrations, contributing to the sharp decline in hepatic glucose production.

Because the lipid bilayers that make up cell membranes are impermeable to carbohydrates, carbohydrate-transport systems are required. In recent years, two distinct molecular families of cellular transporters of glucose (and other hexoses, including fructose and lactose) have been cloned. The sodium-linked glucose transporters are largely restricted to the intestine and kidney, where they actively transport glucose against a glucose-concentration gradient by using sodium cotransport as an energy source.[1] The other group of transporters convey glucose by facilitated diffusion down glucose-concentration gradients. This group consists of five homologous transmembrane proteins, GLUT-1, 2, 3, 4, and 5, that are encoded by distinct genes. The GLUT proteins have distinct substrate specificities, kinetic properties, and tissue distributions that dictate their functional roles (Table 1). Studies that have examined regulation of the expression of glucose-transporter genes as well as cell-biologic characteristics of the GLUT proteins have led to a better understanding of the mechanisms by which carbohydrate metabolism is regulated.

Muscle is the principal site of insulin-stimulated glucose disposal in vivo; less glucose is transported into adipose tissue.[2] Previous studies have indicated that in muscle, glucose transport across the plasma membrane is the rate-limiting step for glucose metabolism in normal subjects[3-5] and in those with diabetes.[6-8] In this issue of the *Journal,* Cline et al.[9] report their use of a novel $^{13}C-^{31}P$ nuclear magnetic resonance approach to demonstrate that glucose transport is the rate-controlling step in skeletal-muscle glucose metabolism in both normal subjects and those with type 2 diabetes. Resistance to the stimulatory effect of insulin on glucose utilization is a key pathogenic feature of obesity, syndrome X (also known as the insulin resistance syndrome and characterized by insulin resistance, dyslipidemia, hypertension, and an increased risk of cardiovascular disease), and most forms of type 2 (non-insulin-dependent) diabetes. To a lesser extent, insulin resistance contributes to the morbidity associated with type 1 (autoimmune) diabetes. The fact that nondiabetic relatives of subjects with type 2 diabetes also have insulin resistance is evidence of its genetic basis.[10] Studies in subjects with either type 1 or type 2 diabetes indicate that the defect lies at the level of glucose transport or glucose phosphorylation.[6,8,11] Now Cline et al. demonstrate that im-

From the Department of Biochemistry and Molecular Biology, University College London, London (P.R.S.); and the Diabetes Unit, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston (B.B.K.). Address reprint requests to Dr. Kahn at the Diabetes Unit, Beth Israel Deaconess Medical Center, 99 Brookline Ave., Boston, MA 02215.

TABLE 1. CHARACTERISTICS OF THE FIVE FACILITATED-DIFFUSION GLUCOSE TRANSPORTERS.*

TRANSPORTER	APPROXIMATE K_m FOR GLUCOSE	TISSUE DISTRIBUTION	CHARACTERISTICS
	mmol/liter		
GLUT-1	20	Widely expressed; high concentrations in brain, erythrocytes, and endothelial cells	Constitutive glucose transporter
GLUT-2	42	Kidney, small intestine epithelia, liver, pancreatic beta cells	Low-affinity glucose transporter; has a role in sensing glucose concentrations in islets
GLUT-3	10	Neurons, placenta	High-affinity glucose transporter
GLUT-4	2–10	Skeletal muscle, cardiac muscle, adipose cells	Insulin-responsive glucose transporter
GLUT-5	NA	Small intestine, sperm, kidney, brain, adipose cells, muscle	Fructose transporter; very low affinity for glucose

*K_m denotes the Michaelis–Menten constant, and NA not applicable.

pairment of insulin-stimulated glucose transport, not impairment of the phosphorylation step, is responsible for resistance to insulin-stimulated glycogen synthesis in muscle in subjects with type 2 diabetes.[9] Hence, impaired glucose transport has a major role in the pathogenesis of type 2 diabetes.

Molecular Mechanisms of Insulin-Stimulated Glucose Uptake

GLUT-4 is the main insulin-responsive glucose transporter and is located primarily in muscle cells and adipocytes. Its Michaelis–Menten constant for glucose is 36 to 179 mg per deciliter (2 to 10 mmol per liter), which is within the range of physiologic blood glucose concentrations, so it can be saturated under ambient conditions. The importance of GLUT-4 in glucose homeostasis is best demonstrated by studies of mice in which one allele of the *GLUT-4* gene has been disrupted. These mice have approximately a 50 percent reduction in GLUT-4 concentrations in skeletal muscle, heart, and adipocytes; they have severe

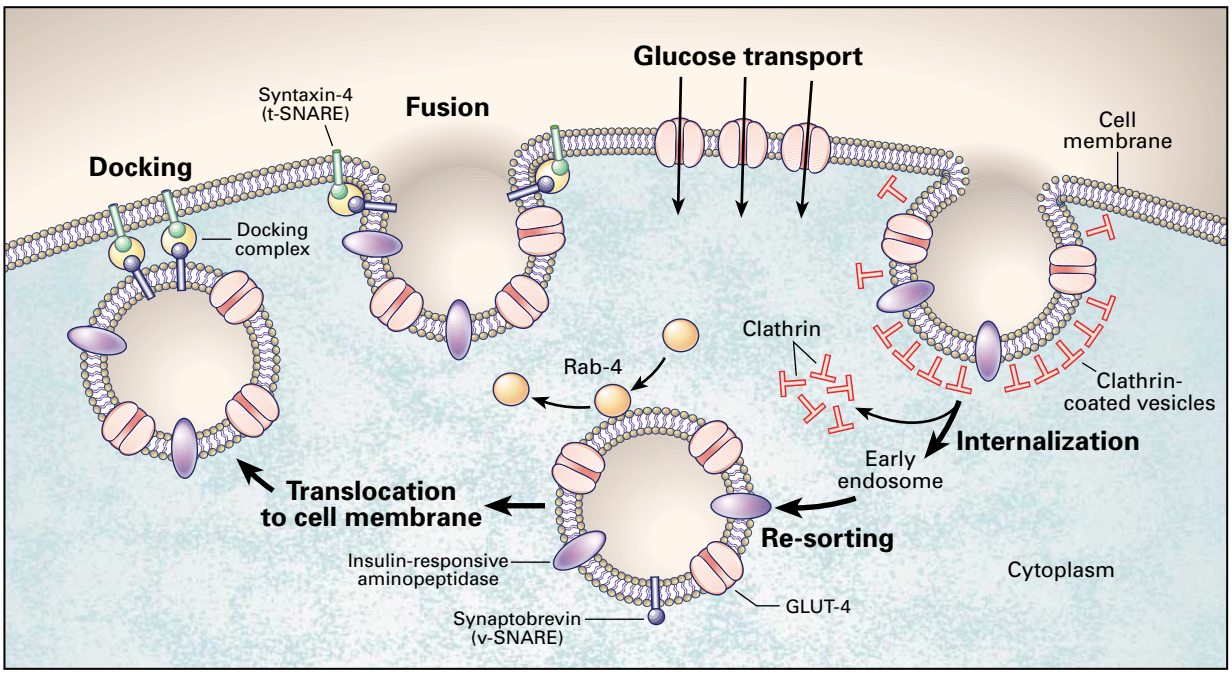

Figure 1. Mechanisms Involved in the Translocation of GLUT-4 Glucose Transporters in Muscle Cells and Adipocytes.

In the absence of insulin, about 90 percent of GLUT-4 is sequestered intracellularly in distinct vesicles that also contain proteins such as insulin-responsive aminopeptidase, synaptobrevin (also known as vesicle-associated membrane protein-2, or v-SNARE), and the small guanosine triphosphate–binding protein Rab-4. In response to insulin, exercise, or contraction, vesicles containing GLUT-4 move to the plasma membrane, where they dock, forming complexes involving syntaxin-4 (also known as target synaptosome-associated protein receptor, or t-SNARE) and synaptobrevin. The vesicles fuse with the plasma membrane, increasing the number of GLUT-4 molecules in the membrane and thus the rate of glucose transport into cells. Rab-4 leaves the vesicle and moves into the cytosol in response to insulin stimulation. On removal of insulin stimulation, GLUT-4 is internalized by the budding of clathrin-coated vesicles from the plasma membrane. GLUT-4 enters early endosomes, from which it is re-sorted to intracellular GLUT-4–containing vesicles.

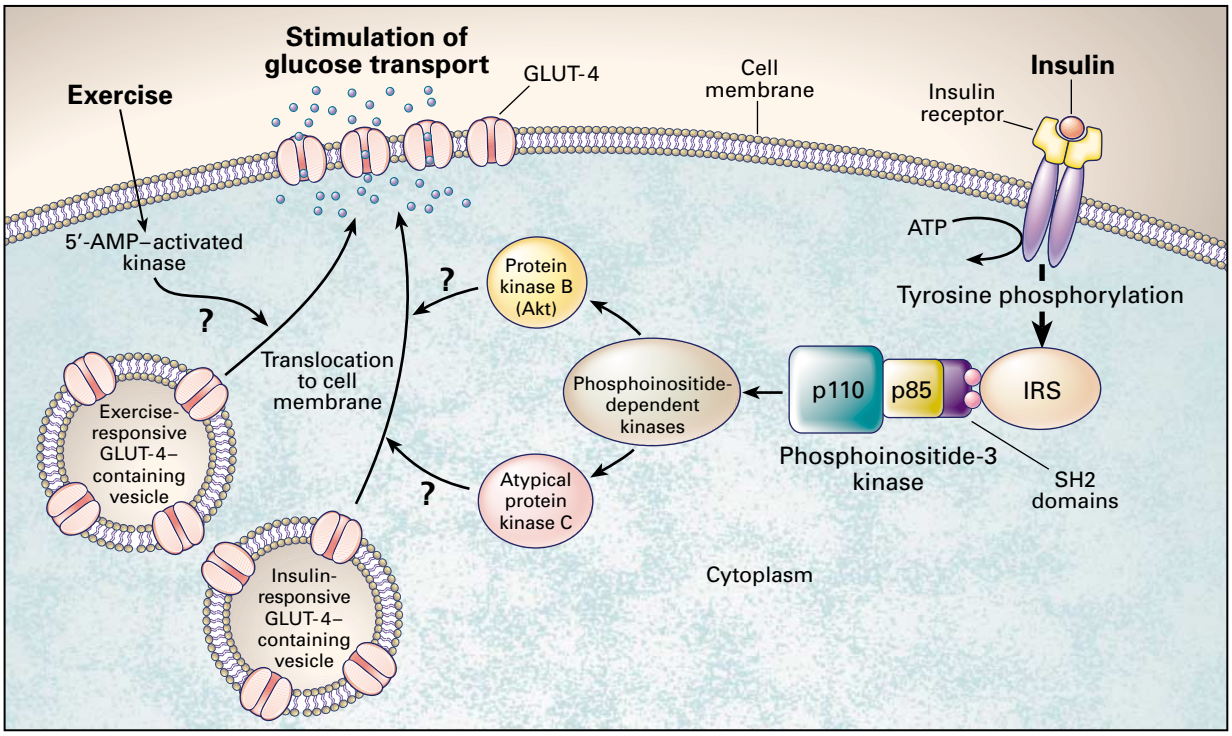

Figure 2. Insulin Signaling Pathways That Regulate Glucose Metabolism in Muscle Cells and Adipocytes.

GLUT-4 is stored in intracellular vesicles. Insulin binds to its receptor in the plasma membrane, resulting in phosphorylation of the receptor and insulin-receptor substrates such as the IRS molecules. These substrates form complexes with docking proteins such as phosphoinositide-3 kinase at its 85-kd subunit (p85) by means of SH2 (Scr homology region 2) domains. Then p85 is constitutively bound to the catalytic subunit (p110). Activation of phosphoinositide-3 kinase is a major pathway in the mediation of insulin-stimulated glucose transport and metabolism. It activates phosphoinositide-dependent kinases that participate in the activation of protein kinase B (also known as Akt) and atypical forms of protein kinase C (PKC). Exercise stimulates glucose transport by pathways that are independent of phosphoinositide-3 kinase and that may involve 5′-AMP–activated kinase.

insulin resistance[12]; and in at least half the males, frank diabetes develops with age.[13]

In normal muscle cells and adipocytes, GLUT-4 is recycled between the plasma membrane and intracellular storage pools. GLUT-4 differs from other glucose transporters in that about 90 percent of it is sequestered intracellularly in the absence of insulin or other stimuli such as exercise (Fig. 1).[14,15] In the presence of insulin or another stimulus, the equilibrium of this recycling process is altered to favor the translocation (regulated movement) of GLUT-4 from intracellular storage vesicles to the plasma membrane and, in the case of muscle, to the transverse tubules as well. The net effect is a rise in the maximal velocity of glucose transport into the cell.[14,15]

Insulin-stimulated intracellular movement of GLUT-4 is initiated by the binding of insulin to the extracellular portion of the transmembrane insulin receptor (Fig. 2). Its binding activates tyrosine kinase phosphorylation at the intracellular portion of the receptor. The chief substrates for this tyrosine kinase include insulin-receptor–substrate molecules (IRS-1, IRS-2, IRS-3, and IRS-4), Gab-1 (Grb2 [growth factor receptor–bound protein 2]–associated binder 1), and SHC (Src and collagen-homologous protein).[16,17] In both adipocytes and skeletal muscle, subsequent activation of phosphoinositide-3 kinase is necessary for the stimulation of glucose transport by insulin[16,17] and is sufficient to induce at least partial translocation of GLUT-4 to the plasma membrane.[18-20] Activation of downstream protein serine–threonine kinases may also be involved.[21] Phosphoinositide-3 kinase also activates these other kinases by generating phosphatidylinositol lipid products in the lipid bilayer of cellular membranes. These lipids, in turn, bring into proximity and thereby activate key signaling molecules. In this way, a serine–threonine kinase called protein kinase B (or Akt) and phosphoinositide-dependent kinase 1 are brought together,[22] allowing the latter to phosphorylate and activate protein kinase B. Some isoforms of protein kinase C are also activated by insulin, and phosphoinositide-dependent protein kinase 1 may contribute to the activation of protein kinase C because it phos-

phorylates a site in the activation loop of protein kinase C.[23]

Intracellular translocation of GLUT-4 to the plasma membrane is stimulated by the expression of active forms of protein kinase B or atypical isoforms of protein kinase C in cultured cells.[24-26] This suggests that one or both of these kinases may be the in vivo mediator of the process in which insulin signals GLUT-4 translocation. The atypical isoforms of protein kinase C are good candidates: it has been found that blocking their action attenuates insulin-stimulated movement of GLUT-4,[25,26] whereas studies in which the activation of protein kinase B is blocked have had conflicting results with regard to GLUT-4 translocation.[27,28] Furthermore, in muscle from diabetic subjects, stimulation of glucose transport is impaired at physiologic insulin concentrations, whereas the activation of protein kinase B is normal.[29]

The functionally important targets further downstream in the phosphoinositide-3-kinase signaling cascade have not been identified, but they may be proteins that regulate the docking of GLUT-4–containing vesicles at the plasma membrane and their fusion with it. Several proteins have been identified in GLUT-4–containing vesicles (Fig. 1), most of which are also present in other exocytotic vesicles such as synaptic vesicles in neurons. One such protein, insulin-responsive aminopeptidase, is of particular interest because it also localizes in GLUT-4–containing vesicles in adipocytes and muscle cells, although its physiologic function is unknown.[30] A model of the docking of GLUT-4 vesicles and their fusion with the plasma membrane has been developed on the basis of mechanisms used by synaptic vesicles. This model proposes that proteins similar to those involved in synaptosome fusion form a specific complex that links the GLUT-4 vesicle with the plasma membrane.[30] Proteins such as Rab-4, a small guanosine triphosphate–binding protein, may modify the retention or movement of the GLUT-4–containing vesicle.

POSSIBLE CAUSES OF RESISTANCE TO THE STIMULATORY EFFECTS OF INSULIN ON GLUCOSE TRANSPORT

Mutations in Glucose Transporters

Mutations in *GLUT-1* are associated with intractable seizures resulting from a reduction in glucose transport across the blood–brain barrier.[31] *GLUT-2* mutations cause the Fanconi–Bickel syndrome, which is a rare, autosomal recessive metabolic disorder characterized by hepatic and renal glycogen accumulation, nephropathy, and impaired utilization of glucose and galactose.[32] Mutations in *GLUT-4* could theoretically cause insulin resistance. However, polymorphisms in the *GLUT-4* gene are very rare in subjects with type 2 diabetes and have the same prevalence among nondiabetic subjects.[33-35]

TABLE 2. REGULATION OF GLUT-4 MESSENGER RNA AND PROTEIN CONCENTRATIONS IN ANIMALS WITH ALTERED SENSITIVITY TO INSULIN.*

ANIMAL MODEL†	FASTING SERUM INSULIN	FASTING SERUM GLUCOSE	GLUT-4 CONCENTRATION	
			MUSCLE	FAT
Zucker obese (*fa/fa*) rats				
Young	↑	↔	↔	↑↑
Old	↑↑	↔	↔	↓↓
Zucker diabetic fatty (*ZDF/drt*) rats	↑	↑↑	↓↓	↓↓
Rats with gold thioglucose–induced obesity	↑↑	↑	↔	↓↓
Diabetic (*KK/A^y*) mice	↑↑	↑	↓↓	↓↓
Viable yellow (*A^{vy}/a*) mice	↑↑	↑	↓↓	↓↓
Brown-fat–ablated mice	↑↑	↑	↔	ND
Obese diabetic (*db/db*) mice	↑	↑	↔	↔
Neuropeptide-injected rats	↑	↔	↔	↑
Rats with VMH-lesion–induced obesity	↑	↔	↔	↑↑, then ↔
Rats with high-fat feeding	↑	↔	↔	↓↓
Dexamethasone-treated rats	↑	↑	↔	ND
Rats and mice with streptozocin-induced diabetes	↓	↑↑	↔	↓↓
Spontaneously hypertensive rats	↑	↔	↔	ND
Aged rats	↑	↔	↓↓	↓↓
Hyperthyroid rats	↓	↔	↑	↑
Hypothyroid rats	↔	↔	↓	ND
Diabetic rats treated with metformin	↓	↓	↔	ND
Rats and mice given leptin	↓	↓	ND	ND
Rats given thiazolidinediones	↓	↓	↔	↑

*Data are adapted from Abel et al.[36] ND denotes not determined, and VMH ventromedial hypothalamus. The symbol ↑ denotes moderately increased, ↑↑ markedly increased, ↔ unchanged, ↓ moderately decreased, and ↓↓ markedly decreased.

†The *fa/fa* rats are obese because of a mutation in the leptin receptor. The *KK/A^y* mice are a cross between the diabetic *KK* mouse and the obese *A^y* (lethal yellow) mouse, which has a mutation in the *agouti* gene. The *A^{vy}/a* mice have obesity and insulin resistance as well as a mutation in the *agouti* gene. The *db/db* mice are obese and diabetic because of a mutation in the leptin receptor.

Tissue-Specific Alterations in GLUT-4 Production

In various insulin-resistant states, expression of the *GLUT-4* gene is regulated differently in muscle and adipose tissue as shown by studies in both animals (Table 2) and humans (Table 3).[36,37] GLUT-4 concentrations are reduced in adipocytes from obese subjects and those with impaired glucose tolerance or type 2 diabetes, but GLUT-4 concentrations are not reduced in skeletal muscle in obese subjects, subjects with type 1 or type 2 or gestational diabetes, or insulin-resistant relatives of subjects with type 2 diabetes.[36,37] Since muscle is the primary site of insulin-stimulated disposal of glucose, the impairment of whole-body insulin sensitivity in these states cannot be explained by a decrease in the production of GLUT-4. In contrast, decreased GLUT-4 production

TABLE 3. CHANGES IN GLUT-4 MESSENGER RNA AND PROTEIN CONCENTRATIONS UNDER VARIOUS CONDITIONS IN HUMANS.*

CONDITION	GLUT-4	
	MUSCLE	ADIPOSE TISSUE
Type 1 diabetes	↔	ND
Pancreatic transplantation in subjects with type 1 diabetes	↓	ND
Type 2 diabetes	↔	↓
Insulin resistance in relatives of subjects with type 1 diabetes	↔	ND
Obesity	↔†	↓
Gestational diabetes	↔	↔ or ↓
Aging	↓	ND
Uremia	↔	ND
Polycystic ovary syndrome	ND	↓
Pseudoacromegaly	↔	ND
Exercise	↑	ND
Sulfonylurea therapy	↔	ND
Weight loss	↔	ND

*Data are adapted from Abel et al.[36] ND denotes not determined. Symbols are explained in the footnotes to Table 2.

†A decrease occurs in morbidly obese subjects.

in muscle with aging in normal subjects may play a part in age-related declines in insulin sensitivity.[36,37]

Although decreased production of GLUT-4 is not the cause of insulin resistance in obesity and diabetes, there may be a therapeutic advantage to increasing the concentrations of GLUT-4 in these conditions. Glucose tolerance and insulin sensitivity are increased by overproduction of GLUT-4 in muscle or adipose tissue, or both, of normal[38-41] or *db/db* obese, diabetic[42] mice. Furthermore, an increase in GLUT-4 reduces hyperglycemia and increases insulin sensitivity in mice with streptozocin-induced diabetes.[40,43] Exercise training increases both GLUT-4 concentrations and insulin sensitivity in muscle from initially sedentary middle-aged subjects, older subjects with insulin resistance, and subjects with type 2 diabetes.[44]

Defects in the Intracellular Translocation of GLUT-4

The reduction in insulin-stimulated glucose uptake in skeletal muscle in obese subjects and those with diabetes is associated with an impairment in insulin-stimulated movement of GLUT-4 from intracellular vesicles to the plasma membrane.[45] Since GLUT-4 concentrations are normal in skeletal muscle in these subjects, the most likely explanation for the insulin resistance is a defect in the insulin-signaling pathways that regulate the translocation of GLUT-4 (Fig. 2) or in the molecular machinery directly involved in the recruitment of GLUT-4–containing vesicles to the plasma membrane, their docking, and their fusion with the membrane (Fig. 1).[30] There is evidence of at least two distinct intracellular pools of recruitable GLUT-4 in muscle, and GLUT-4 in at least one of the pools can respond to stimuli other than insulin in subjects with insulin resistance. Stimuli such as muscle contraction and hypoxia activate pools distinct from that activated by insulin, and the glucose-uptake response to exercise and hypoxia is normal in muscle from obese subjects and those with diabetes.[43] GLUT-4–containing vesicles also appear to be normal: glucose transport in insulin-resistant muscle is activated normally by inhibitors of both serine–threonine phosphatases (e.g., okadaic acid[21]) and tyrosine phosphatases (e.g., vanadate[21]). Both classes of phosphatase inhibitors are thought to prolong the activation of distal components of the insulin-signaling cascade.

Defects in Signaling Pathways

Attention has focused on phosphoinositide-3 kinase because of its central role in insulin-stimulated intracellular translocation of GLUT-4. Activation by insulin of phosphoinositide-3 kinase in muscle is reduced in severely obese subjects with insulin resistance[46] and those with diabetes,[47] and expression of the regulatory subunit of phosphoinositide-3 kinase is reduced in those who are morbidly obese.[46] However, the main defects in signaling may be proximal in sequence to the activation of phosphoinositide-3 kinase, because concentrations of phosphorylated insulin receptor and of IRS-1 are also decreased in muscle from morbidly obese subjects[46] and those with diabetes.[47]

Impairment of insulin-stimulated glucose uptake may also result from the up-regulation of proteins that inhibit the signaling pathways. The expression and activity of several protein tyrosine phosphatases are increased in skeletal muscle and fat in obese subjects but not in those with type 2 diabetes.[48] Knockout of the gene for one of these phosphatases in transgenic mice increases insulin signaling and prevents both the insulin resistance and the obesity that usually occur with a high-fat diet.[49] Another candidate may be the 15-kd substrate of protein kinase C, described as "phosphoprotein enriched in diabetes," which is overexpressed in insulin target tissues in both obese subjects and those with diabetes.[50] Overexpression of this protein in cultured cells attenuates insulin-stimulated GLUT-4 translocation and thus attenuates insulin-stimulated glucose transport. Overexpression of Rad, a small guanosine triphosphate–binding protein, also inhibits GLUT-4 translocation in cultured cells,[51] although there is controversy over whether Rad expression is increased in muscle in type 2 diabetes.[52,53]

These findings suggest that insulin resistance may be overcome by increasing insulin signaling — for example, by reducing the activity of molecules that normally attenuate the action of insulin, such as the tyrosine phosphatases. Vanadate, which inhibits tyro-

sine phosphatases, stimulates glucose transport by increasing the translocation of GLUT-1 and GLUT-4 in muscle and fat cells. Several organo-vanadium compounds have been found to improve insulin sensitivity in both muscle and liver in subjects with type 2 diabetes and to reduce insulin requirements in those with type 1 diabetes.[54]

Impairment of Insulin-Stimulated Glucose Transport by Circulating or Paracrine Factors

Free Fatty Acids

The chronic elevation of serum free-fatty-acid concentrations in many subjects with obesity or diabetes may contribute to the decreased uptake of glucose into peripheral tissues.[55-58] In humans, lipid infusion for four hours decreases insulin-stimulated glucose uptake into muscle in association with a loss of the ability of insulin to stimulate phosphoinositide-3 kinase activity.[59] The latter could lead to defective translocation of GLUT-4. In rodents, a high-fat diet can induce insulin resistance through a combination of reduced GLUT-4 expression in adipocytes[36] and impaired insulin-stimulated translocation of GLUT-4 in skeletal muscle, as a result of defective insulin signaling by phosphoinositide-3 kinase.[60] The defect in signaling may be caused by free-fatty-acid–induced diversion of glucose into the hexosamine pathway (see below).[61] Despite the impaired action of insulin in animals given high-fat diets, glucose transport in muscle is activated normally by hypoxia and by agents that stimulate the release of calcium from the sarcoplasmic reticulum.[60]

Glucose Toxicity and the Hexosamine Pathway

Hyperglycemia itself has detrimental effects on insulin secretion and on the action of insulin in peripheral tissues.[62] In vitro incubation of muscle strips with high concentrations of glucose leads to a reduction in insulin-stimulated glucose uptake.[63] However, glucose-induced impairment of the action of insulin can be reversed by restoring normal glucose concentrations, suggesting that tight control of blood glucose concentrations in subjects with diabetes can probably improve insulin resistance in muscle.

The mechanism of glucose toxicity in muscle may involve the hexosamine pathway,[64] in which the enzyme glutamine:fructose-6-phosphate amidotransferase diverts glucose from the glycolytic pathway at the level of fructose-6-phosphate, resulting in the production of glucosamine-6-phosphate and, subsequently, other hexosamine products.[64] Exposure of muscle to glucosamine reduces stimulation by insulin of glucose transport and GLUT-4 translocation.[65,66] Transgenic mice that overexpress glutamine:fructose-6-phosphate amidotransferase are resistant to the effects of insulin on glucose uptake in muscle.[67] The potential relevance of these models to our understanding of insulin resistance in humans is demonstrated by the finding that the activity of glutamine:fructose-6-phosphate amidotransferase is also increased in skeletal muscle in subjects with diabetes.[68]

Tumor Necrosis Factor α

The cytokine tumor necrosis factor α (TNF-α) has potent inhibitory effects on insulin signaling in isolated muscle and adipose tissue.[69] Serum TNF-α concentrations in both lean and obese subjects are very low, suggesting that TNF-α secreted by muscle cells[70] and adipocytes[69] acts in a paracrine manner. The finding that TNF-α expression is high in muscle and fat in obesity and diabetes led to the hypothesis that it may cause insulin resistance in vivo. Support for this possibility comes from studies of genetically obese Zucker (*fa/fa*) rats in which systemic administration of monoclonal antibodies that neutralize TNF-α reversed insulin resistance.[69] However, the administration of similar antibodies to subjects with type 2 diabetes did not result in an improvement in insulin resistance.[71]

NON–INSULIN-MEDIATED STIMULATION OF GLUCOSE UPTAKE IN MUSCLE AND FAT

Although insulin is the chief acute physiologic stimulus of glucose disposal, other stimuli can also activate glucose uptake and intracellular translocation of GLUT-4 to the cell membrane.

Exercise

Bouts of exercise stimulate translocation of GLUT-4 to the plasma membrane and increase glucose transport in skeletal muscle.[44] The signals that mediate exercise-induced GLUT-4 recruitment differ from those that mediate insulin-induced recruitment, in that phosphoinositide-3-kinase activity is not required for the exercise effect.[72] Instead, activation of the 5′-AMP–activated kinase may have a role (Fig. 2).[73] The exercise-induced stimulation of GLUT-4 translocation is normal in insulin-resistant subjects. Thus, exercise has a therapeutic effect on control of glycemia in subjects with diabetes.[44] Furthermore, regular physical activity decreases the risk of type 2 diabetes in subjects who are at high risk for the disease.[44]

Nitric Oxide and Bradykinin

Exercise-induced production of nitric oxide and subsequent production of cyclic guanosine monophosphate may be involved in the regulation of glucose transport in muscle, independently of the effects of nitric oxide on vasodilatation.[74] Bradykinin may also play a part in exercise-induced glucose transport, since it is released from muscle during exercise and, in cells that express bradykinin receptors, it stimulates GLUT-4 translocation.[75] Muscle has high levels of bradykinin receptors, and as with the glucose uptake stimulated by exercise, bradykinin-stimulated

glucose uptake is not blocked by inhibitors of phosphoinositide-3 kinase.[75]

Insulin-Like Growth Factors

Both insulin-like growth factor I and insulin-like growth factor II (IGF-I and IGF-II) have a high degree of sequence homology with insulin. Furthermore, the IGF-I receptor is highly homologous to the insulin receptor, and the intracellular signaling pathways activated by these receptors are very similar. Both IGF-I and IGF-II have insulin-like effects on glucose transport in muscle and adipocytes in vitro.[76-78] IGF-I causes translocation of GLUT-4 to the muscle cell surface in vitro,[76] and its administration in vivo has a potent hypoglycemic effect.[79] Serum concentrations of free IGF-I and IGF-II are normally very low, because they are sequestered by specific binding proteins. Recent evidence suggests that alterations in the serum concentrations of these proteins, as in uncontrolled type 1 diabetes, may affect glucose homeostasis.[79] IGF-I bypasses defects at the level of the insulin receptor and effectively lowers blood glucose concentrations in some subjects with severe insulin-resistance syndromes of various causes, including mutations in the insulin receptor, and in subjects with type 1 or type 2 diabetes.[79]

C Peptide

C peptide, which is released by the processing of proinsulin into mature insulin in pancreatic beta cells, also increases glucose uptake into skeletal muscle in both normal subjects and subjects with type 1 diabetes.[80] It does not act through the insulin receptor.[80] However, C peptide probably does not have a role in the treatment of insulin resistance, since serum concentrations are high in many insulin-resistant subjects, yet these high values are not sufficient to normalize glucose disposal.

Leptin

Leptin, the protein product of the *ob* gene,[81] is a hormone that is secreted by adipocytes. It serves as an "adipostat," signaling the brain in response to changes in energy stores.[82] The primary site of leptin's action is thought to be the hypothalamus, but it also has functions in peripheral tissues. Administration of leptin to normal, genetically obese, or diabetic rodents improves sensitivity to insulin and reduces hyperinsulinemia before any changes in food intake or body weight occur.[83-85] Although this rapid increase in insulin sensitivity may be due to an increase in glucose disposal in skeletal muscle and brown adipose tissue, the effect is indirect, since leptin does not directly increase glucose transport in muscle or adipocytes.[82,85-89] Indirectly, however, leptin-induced increases in fatty acid oxidation[87] could improve glucose uptake. Whether the effects on glucose metabolism in insulin-sensitive tissues are mediated indirectly through the brain and sympathetic nervous system is controversial.[85,90] The administration of leptin may also increase insulin sensitivity as a result of changes in physical activity, thermogenesis, serum concentrations of substrates such as fatty acids,[83] and glucose flux in the liver.[90]

Thyroid Hormone

The rate of glucose transport into muscle and fat is also affected by levels of thyroid hormone. Administration of thyroid hormone to normal animals for several days increases both basal and insulin-stimulated glucose uptake into muscle and adipocytes, at least partly as a result of increases in GLUT-4 expression.[36,37] In obese Zucker rats, the administration of thyroid hormone is associated with total amelioration of hyperinsulinemia.[37]

EFFECTS OF DRUG THERAPY OF DIABETES ON GLUCOSE TRANSPORT

Sulfonylureas

The main therapeutic effect of sulfonylureas is the potentiation of insulin secretion by augmentation of potassium-channel activity in pancreatic islet cells.[91] By facilitating the translocation of both GLUT-4 and GLUT-1 to the cell surface,[92] these drugs can also increase glucose transport in adipocytes that have been rendered insulin resistant in vitro.[92] In vivo studies have not distinguished the potentially direct effects of the sulfonylureas on peripheral tissues from the indirect effects produced by reversal of glucose toxicity as a result of improved insulin secretion.

Biguanides

Although the liver is the primary site of action of the biguanide drugs such as metformin, in vivo studies indicate that metformin also increases glucose uptake into peripheral tissues.[93] Metformin has also been found to have short-term insulin-like effects on glucose transport and GLUT-4 translocation in adipocytes[94] and muscle in vitro.[95,96] However, the concentration of the drug required for these in vitro effects is at least an order of magnitude greater than that required for a clinical effect. Therefore, it is unlikely that acute stimulation of GLUT-4 translocation is an important mechanism by which metformin improves hyperglycemia in diabetes.

Thiazolidinediones

Thiazolidinediones are a new class of insulin-sensitizing drugs that increase the disposal of glucose in peripheral tissues in animals and humans with insulin resistance, including subjects with type 2 diabetes and women with the polycystic ovary syndrome.[97-99] Treatment of insulin-resistant rodents with thiazolidinediones restores the expression and translocation of GLUT-4 in adipocytes.[97,98,100,101] Thiazolidinediones also overcome the TNF-α–induced inhibition of in-

sulin-stimulated glucose transport in adipocytes.[102] In insulin-resistant rats given high-fat diets and insulin-deficient rats with streptozocin-induced diabetes, thiazolidinedione treatment increases insulin-stimulated glucose uptake in muscle.[97,98,100] Thiazolidinediones do not increase the expression of GLUT-4 in rodent muscle or human muscle cells, although they do induce the expression of GLUT-1.[98,100,101] Furthermore, thiazolidinediones do not restore defective insulin-stimulated GLUT-4 translocation in muscle in insulin-resistant Zucker rats.[103] Thus, the cellular mechanism by which thiazolidinediones increase glucose uptake in muscle in vivo is uncertain.

CONCLUSIONS

Insulin resistance is a major factor in the pathogenesis of obesity, diabetes, and the insulin-resistance syndrome and is associated with an increased risk of cardiovascular disease. In skeletal muscle, insulin resistance may be caused by defects in glucose transport, which result from impairments in the translocation, fusion, or exposure and activation of GLUT-4 glucose transporters. These abnormalities in GLUT-4 translocation in muscle appear to result from defects in intracellular signaling. These defects may be inherent in the tissue or may be due to circulating or paracrine factors such as hyperglycemia itself (glucose toxicity) or increased serum concentrations of free fatty acids or TNF-α. Insulin-stimulated glucose uptake in adipocytes is also defective, largely as a result of the down-regulation of *GLUT-4* expression. Studies in transgenic mice indicate that increased intracellular concentrations of GLUT-4 can ameliorate diabetes.

Drugs that increase insulin sensitivity, such as metformin and thiazolidinediones, can improve glycemic control in subjects with type 2 diabetes, and insulin-sensitizing drugs with various mechanisms of action have additive effects. Because the impairment in insulin-stimulated glucose transport in subjects with type 2 diabetes can be bypassed by other stimuli, such as exercise and hypoxia, a greater understanding of the intracellular signaling pathways by which these stimuli increase GLUT-4 translocation could lead to new approaches to the treatment of insulin resistance. Therapies that improve the recruitment of glucose transporters to the cell surface are likely to reduce the morbidity associated with type 2 diabetes and obesity and may prevent the development of frank diabetes in people at high risk.

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