GLUT12: a second insulin-responsive glucose transporters as an emerging target for type 2 diabetes

Insulin resistance plays a major role in the pathogenesis of type 2 diabetes mellitus. The need for an effective treatment for type 2 diabetes mellitus has, therefore, become increasingly important. The ability of insulin to stimulate glucose uptake into muscle and adipose tissue is important for the maintenance of whole-body glucose homeostasis. Glucose uptake in mammalian cells is mediated by a family of highly related facilitative glucose transporters (GLUT), and until now, 13 GLUT isoforms have already been identified in human, with their tissue specificity extensively studied. Members of the GLUT family exhibit distinct glucose transport kinetic capabilities and tissue-specific patterns of expression that reflect energy requirements and metabolism. The insulin-regulated glucose transporter GLUT4 is expressed mainly in insulin-responsive tissues, i.e. white and brown adipose tissue, and in heart and skeletal muscles, where it mediates glucose uptake in response to acute insulin stimulation. Insulin resistance occurs partially from defective GLUT4 expression and trafficking, and as a result, blood glucose can rise to pathological levels. GLUT4 mRNA and protein are downregulated in adipose tissue in the setting of obesity and type 2 diabetes mellitus, in both rodents and humans. In contrast, skeletal muscle GLUT4 expression remains intact in these conditions, but alterations in the distribution of GLUT4 between intracellular membranes and the plasma membrane and in insulin-stimulated translocation of GLUT4 to the plasma membrane results in impaired glucose transport.

More than a decade ago, a GLUT4 knockout mouse was developed, and its phenotype was characterized. Surprisingly, the GLUT4 null mouse does not develop hyperglycemia1, and the soleus muscle from GLUT4 knockout mice retains its ability to increase the glucose uptake in response to insulin2. This evidence suggests that insulin-sensitive GLUT, rather than GLUT4, may exist.

In a recent article, Purcell et al.3 generated a transgenic mouse that overexpressed GLUT12 under a β-actin promoter and showed that the increased expression of GLUT12 enhanced whole-body insulin sensitivity through an increased glucose clearance rate in insulin-sensitive tissues. GLUT12 is a member of class III glucose transporters, which preferentially transports D-glucose and 2-deoxy-D-glucose over other hexoses4. The presence of targeting motifs similar to GLUT4 and GLUT8, and localization primarily in insulin-sensitive tissues, has led to research to clarify whether GLUT12 may represent a second insulin-sensitive GLUT. In human skeletal muscle, GLUT12 translocates to the plasma membrane following euglycemic insulin infusion5. To further assess the function of GLUT12 as an insulin-sensitive GLUT, Purcell et al. generated GLUT12 transgenic (TG) mice and analyzed the effects of GLUT12 overexpression on whole-animal glucose homeostasis and insulin-stimulated glucose clearance into peripheral tissues.

GLUT12 overexpression was greatest in the brain and heart, followed by the soleus, fat, extensor digitorum longus (EDL) and liver. In the insulin-sensitive tissues, increased GLUT12 expression ranged from 40% in the EDL to 75% in the heart. GLUT12 overexpression did not alter expression of GLUT4 in skeletal muscle and fat nor did it affect fasting glucose, but it decreased fasting insulin, suggesting improved insulin sensitivity. During glucose tolerance tests, TG mice exhibited a more rapid normalization of blood glucose than wild-type mice, consistent with enhanced insulin sensitivity.

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Enhanced insulin sensitivity was more directly shown in the insulin tolerance tests. Compared with wild-type mice, TG mice had a greater decrease in blood glucose concentration after administering insulin. The hyperinsulinemic-euglycemic clamp confirmed enhanced insulin sensitivity, because mice that overexpressed GLUT12 required a 70% greater glucose infusion rate than wild-type mice to maintain an equal degree of euglycemia. Enhanced GLUT12-mediated glucose clearance demonstrated tissue specificity. In response to insulin infusion, glucose clearance was consistently twofold greater in TG than the wild-type mice in the EDL, soleus and fat, but not in the heart, despite the relative higher degree of cardiac GLUT12 overexpression.

This important study indicated that GLUT12 might be a part of a second insulin-responsive glucose transport system in muscle and fat (Figure 1), and activation of GLUT12 can become a new hypoglycemic agent to treat type 2 diabetes mellitus. However, there are many basic and clinical questions requiring more detailed investigation, such as ‘How is the gene expression controlled and protein levels regulated for GLUT12?’, ‘Are GLUT4 and GLUT12 are in the same vesicle or separate vesicles that are translocated by similar pathways of insulin action?’, ‘Are there any metabolic states that modulate GLUT12 gene expression?’, or ‘Does the obesity affect signaling mechanisms that regulate the gene expression and/or subcellular localization of GLUT12?’ The importance of this gene in glucose uptake as an insulin-responsive GLUT awaits further analysis in mice that lack the GLUT12 gene. Further unveiling of the mechanism(s) that regulate GLUT12 gene expression and trafficking in diabetes and obesity will hopefully result in effective ways to overcome insulin resistance and provide a basis of beneficial treatment of type 2 diabetes mellitus.

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