Hypothesis

Insulin-independent glucose transport regulates insulin sensitivity

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Abstract The glucose transport proteins (GLUT1 and GLUT4) facilitate glucose transport into insulin-sensitive cells. GLUT1 is insulin-independent and is widely distributed in different tissues. GLUT4 is insulin-dependent and is responsible for the majority of glucose transport into muscle and adipose cells in anabolic conditions. We suggest the hypothesis that insulin resistance is dependent on whether glucose is entering through GLUT1 or GLUT4 and on the two functional compartments of glucose 6-phosphate formation within the cell. Glucose entering the muscle cell through GLUT4 and phosphorylated by hexokinase II is mainly directed to glycogen synthesis and glycolysis. If glucose is entering through GLUT1 and phosphorylated by hexokinase I, the glucose 6-phosphate so formed is available for all metabolic pathways, including the hexosamine pathway. Hexosamines have a negative feedback effect on GLUT4, and reduced GLUT4 activity decreases insulin-mediated glucose uptake. Thus, insulin-independent glucose transport through GLUT1 can meet the basal needs of the muscle cell. If glucose entrance through GLUT1 and the activation of the hexosamine pathway is abundant, it can decrease the insulin-mediated glucose transport through GLUT4 leading to insulin resistance.

Key words: Glucose transport; Insulin sensitivity; Hexosamine; Glucose transport protein

1. Phylogeny and structure of glucose transport proteins

Glucose is a vital fuel for microorganisms and nearly all cell types in humans. Glucose transport into the cell is catalyzed by transport proteins. Even *Escherichia coli*, which does not have insulin, has two proton-sugar symporters, proton-xylose and proton-arabinose. They share 20–25% amino acid sequence identity with mammalian glucose transporters [1]. In mammalian cells there are at least six facilitative glucose transporters, which are products of a gene family and have specific functions and sites of expression [2]. Glucose transporter 1 (GLUT1) is the predominant facilitative glucose transporter and it is widely distributed in different tissues. GLUT1 is highly conserved with 98% identity in the amino acid sequence between humans and the rat [2]. GLUT4 is insulin-sensitive and it is the predominant glucose transporter in the muscle and adipose tissue. There is 95% sequence identity between human and rat GLUT4 [2], whereas human GLUT1 and GLUT4 have 65% identity.

GLUT1 seems to be coupled with hexokinase I, and GLUT4 with hexokinase II (Fig. 1). Fetal muscle expresses GLUT1 and hexokinase I [3,4], whereas GLUT4 and hexokinase II become predominant in the muscle postnatally [3,4]. The appearances of GLUT4 and hexokinase II in skeletal muscle are coordinated and concomitant with insulin sensitivity in young rats [3,4]. Insulin increases the transcription of muscle hexokinase II, but has no effect on hexokinase I [4–6], which is ubiquitous and is found in almost all cells [5].

2. Why insulin-dependent and -independent transporters?

GLUT4 coupled to hexokinase II facilitates the metabolism or storage of glucose in the muscle and in the adipose tissue in insulin-stimulated conditions, such as after a meal. Another example of the coupling of GLUT4 and insulin action is a well trained athlete, in whom elevated muscle GLUT4 content is associated with increased insulin-stimulated glucose disposal (insulin sensitivity) [7]. Thus, GLUT4 is insulin-dependent and mediates the insulin-stimulated glucose disposal in muscle tissue.

GLUT1 protein may be responsible, at least in part, for the constitutive, insulin-independent glucose uptake in all cells including muscle [2]. In addition to its traditional role, muscle tissue has other functions, such as a role in immunology. The amino acid glutamine is synthesized from glucose in the skeletal muscle [8,9]. Continuous maintenance of a sufficient glutamine concentration in the blood is necessary for the proper functioning of the immune system and survival [10]. This is especially the case during infections, when macrophages need

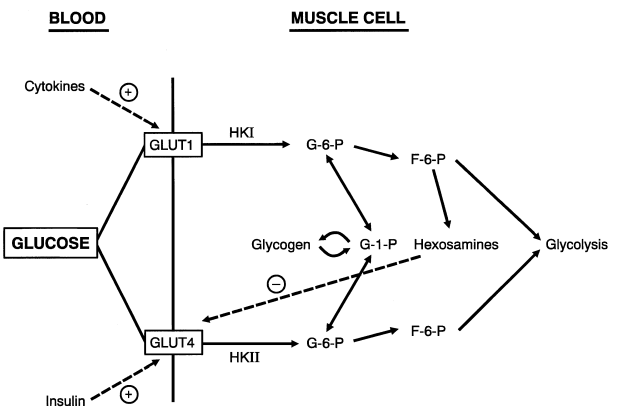

Fig. 1. Glucose transport into muscle cell is mediated by two glucose transport proteins: insulin-independent GLUT1 and insulin-dependent GLUT4. If glucose is transported though the GLUT1 pathway, it is further metabolized by hexokinase I via glucose 6-phosphate (G-6-P) and fructose 6-phosphate (F-6-P) also to hexosamines. These can reduce GLUT4 activity resulting in a decrease in insulin-mediated glucose disposal or insulin resistance.

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glutamine [10]. Intramuscular glucose is used for RNA synthesis through the pentose phosphate pathway, and through the hexosamine pathway for the synthesis of glycoproteins and for the transcriptional control of some genes [11]. These metabolic reactions need a continuous fuel flux that is independent of nutritional status and insulin secretion.

3. Overexpression of GLUT1 and GLUT4

In transgenic mice overexpression of GLUT1 in skeletal muscle leads to fasting hypoglycemia, increased glucose uptake without a rise in plasma insulin and diminishes the blood glucose increment after an oral glucose load [12]. In addition, in these animals muscle glycogen and free glucose concentrations are elevated [13]. However, insulin-stimulated glucose uptake is reduced by nearly 50% [14,15]. GLUT4 overexpression in mice leads to fasting hypoglycemia, reduced rise in blood glucose after an oral glucose load and elevated muscle glycogen concentrations [16]. Insulin sensitivity in these animals is increased by 40–50% [14,15]. Thus, glucose entrance into muscle cells through overexpressed GLUT1 leads to insulin resistance, whereas overexpression of GLUT4 enhances insulin sensitivity.

4. Hexosamines – a signal between GLUT1 and GLUT4

In healthy rats, the infusion of fatty acids, glucosamine or uridine, or hyperglycemia as such all increase the muscle UDP-*N*-acetylglucosamine concentration, which is an index of glucose metabolism through the hexosamine pathway. Each of these factors also causes insulin resistance and reduces insulin-stimulated glycogen synthesis in muscle cells [17]. When glucosamine and uridine are infused simultaneously they have an additive effect in increasing muscle UDP-*N*-acetylglucosamine levels and in causing insulin resistance [18]. A rise in glucosamine availability increases glucosamine incorporation into skeletal muscle GLUT4-containing vesicles reducing their activity [18]. In GLUT1 transgenic mice the 50% decrease in insulin sensitivity is associated with a rise in muscle UDP hexosamines. Thus, a rise in muscle hexosamine concentration causes insulin resistance, probably through a negative feedback effect on GLUT4 vesicles (Fig. 1).

In contrast, in GLUT4 transgenic mice with 40% increase in insulin-stimulated glucose uptake the muscle hexosamine concentration remains unaltered [15]. Similarly, in rats a 6 h hyperinsulinemic stimulation of glucose uptake has no effect on muscle UDP-*N*-acetylglucosamine concentration despite increased muscle glucose uptake [19]. Thus, when the increased glucose uptake in these conditions probably occurs through the insulin-sensitive GLUT4, it has no influence on muscle hexosamine concentration.

In healthy relatives of type 2 diabetic patients insulin-stimulated glucose uptake is decreased, but their glucose effectiveness (as determined by an intravenous glucose tolerance test) is increased [20]. It is possible that the glucose uptake, which is stimulated by acute hyperglycemia, is mediated mainly through GLUT1. Thus, the predominance of glucose transport between GLUT4 and GLUT1 may change depending on the conditions. There are no data on whether changes in the glucose transport routes occur similarly in the fasting state as they seem to happen under stimulated conditions.

5. Insulin resistance in obesity, inflammation or hyperglycemia

In humans insulin resistance is caused by three main factors: obesity [21], inflammation or infections [22,23] and hyperglycemia per se [24]. Obesity is often associated with elevated serum free fatty acid concentrations and enhanced lipid oxidation [25]. This may cause insulin resistance via inhibition of pyruvate dehydrogenase and phosphofructokinase, directing glucose into the hexosamine pathway [17]. Inflammation is characterized by increased concentrations of cytokines, such as tumor necrosis factor α (TNF-α) or interleukin (IL) 1. Cytokines downregulate GLUT4, upregulate GLUT1 [26,27] and stimulate hexose transport in fibroblasts or in rat adipose cells [28–30]. Hyperglycemia increases glucose flux into muscle cell by the mass action effect. This effect is insulin-independent and therefore probably occurs through GLUT1. Obese and type 2 diabetic patients also have a reduced insulin-induced expression of hexokinase II [6]. Thus, the common feature for the insulin resistance induced by obesity, inflammation and infection or hyperglycemia is enhanced glucose transport through GLUT1 and availability for the formation of hexosamines. These can reduce muscle GLUT4 and hexokinase II activity leading to a decrease in insulin-mediated glucose transport (Fig. 1). Troglitazone, which improves insulin sensitivity in type 2 diabetic patients, can prevent hyperglycemia-induced but not glucosamine-induced insulin resistance, suggesting that it has an effect somewhere between GLUT1 and hexosamines (Fig. 1) [31].

Insulin resistance is a common factor in both type 2 diabetic patients and patients with cardiovascular disease [32]. Type 2 diabetic patients are characterized by chronically elevated concentrations of acute-phase serum proteins and cytokines, such as haptoglobin, α1-acid glycoprotein, C-reactive protein or IL-6 [33,34]. Similar results have been reported also in glucose intolerance [33]. There is increasing evidence that a chronic inflammation contributes to the development of atherosclerosis [35]. In both conditions increased cytokine action can lead to glucose transport through GLUT1 and the hexosamine pathway reducing the insulin-mediated glucose transport through GLUT4.

Nitric oxide (NO) may also play a role. The NO donor sodium nitroprusside (SNP) stimulates rat skeletal muscle glucose transport, and increases cell surface GLUT4 concentration [36]. The effects of SNP and insulin on glucose transport are additive at physiological insulin concentrations [37]. However, production of NO by the cytokine-inducible NO synthase in rat skeletal muscle is associated with decreased insulin-stimulated glucose transport [38]. Also a high glucose concentration, which reduces insulin-stimulated glucose uptake in muscle, increases NO generation in human aortic endothelial cells [39]. In L6 myocytes the cytokine-induced increase in glucose uptake is totally prevented by the inhibition of NO synthase [40]. Furthermore, recent in vitro data suggest that thiazolidinediones, insulin-sensitizing agents, inhibit the production of inflammatory cytokines as well as downstream markers of inflammation such as NO elaborated by monocytic cells [41,42]. In humans recent data suggest that NO levels are elevated in first-degree relatives of type 2 diabetic patients [43]. These patients have a reduced insulin-mediated glucose disposal (via GLUT4) and an increased glucose effectiveness (via GLUT1?) [20].

It is thus possible that NO is involved in glucose transport

via both GLUT4 and GLUT1 pathways. The transport via GLUT1 may involve increased production of NO caused by factors such as cytokines or hyperglycemia. If transport via GLUT1 is stimulated, it can reduce glucose transport via GLUT4. If the contribution of deleterious NO is reduced, as occurs after inflammation or during thiazolidinedione therapy, this can enhance insulin-stimulated transport through GLUT4.

This hypothesis can also explain why impaired glucose tolerance or insulin resistance paradoxically may be associated with fasting hypoglycemia. Chronic IL-1β infusion in rats resulted in fasting hypoglycemia and elevated blood glucose levels in response to oral glucose [44]. Anabolic steroids can induce the production of inflammatory cytokines IL-1β and TNF-α from human peripheral blood lymphocytes [45], and methanedienone administration in humans can lower fasting blood glucose concentration, but reduce both oral and intravenous glucose tolerance [46]. These observations can be explained by increased glucose transport through GLUT1 in a fasting state, and decreased GLUT4 action during hyperinsulinemia.

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