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Insulin resistance due to hyperglycaemia: an adaptation protecting insulin-sensitive tissues

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Chronic hyperglycaemia is a cause of diabetic complications in non-insulin-dependent tissues such as the retina, nervous tissue and the kidney [1]. Epidemiological studies have also established an independent relationship between hyperglycaemia and atherosclerosis in coronary and cerebral blood vessels [2, 3]. An increased flux of glucose via non-insulin-dependent mechanisms into the latter tissues, especially endothelial cells, is considered to underlie the adverse consequences of hyperglycaemia [4]. The only tissues which are apparently spared from hyperglycaemia-dependent complications are the brain, where glucose flux is not increased by hyperglycaemia, and insulin-sensitive tissues such as skeletal muscle. The ensuing discussion will present the reasoning underlying the idea that lack of glucose-dependent complications in skeletal muscle is the consequence of normal glucose flux in this tissue, and that this normality can only be achieved at the expense of limiting insulin-stimulated glucose uptake under hyperglycaemic conditions. We will discuss the following arguments: 1) glucose uptake is increased basally but normal after food in insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM); 2) chronic hyperglycaemia is an important determinant of insulin resistance in IDDM and NIDDM; 3) hyperglycaemia-induced insulin resistance is the consequence of overactivity of the hexosamine pathway.

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; CFA, glutamine: fructose 6-phosphate amidotransferase.

Glucose uptake is increased basally but normal postprandially in IDDM and NIDDM

Fasting glycaemia. Direct measurements of glucose uptake across limb tissues have shown that the rate of glucose uptake is linearly related to the fasting plasma glucose concentration [5]. It follows that normalization, i.e. a decrease in basal glucose utilization, is an expected effect of a therapeutic intervention, which lowers the blood glucose concentration. This seems to happen since rates of glucose utilization decrease in patients with NIDDM after treatment with insulin, sulfonylureas, and weight loss (see [6] for review).

Postprandial glycaemia. After ingestion of a mixed meal [7, 8], or oral glucose [9], a similar [9] or even increased [8] fraction of glucose is taken up by the splanchnic bed in patients with NIDDM compared to normal subjects [7, 8, 10]. Exogenous glucose appears in the systemic circulation at comparable rates in patients with NIDDM and in normal subjects [9]. The various hormonal and other signals elicited by the meal (hyperinsulinaemia, hyperglycaemia, suppression of glucagon secretion, neural signals) [11] act in concert to suppress endogenous glucose production efficiently in normal subjects. This suppression is markedly impaired in NIDDM [9] and the predominant cause of postprandial hyperglycaemia [9]. Postprandially, the rate of glucose uptake, in absolute terms, is, however, unaltered in NIDDM, because hyperglycaemia itself is a potent stimulator of glucose uptake [7-9]. Any excess glucose produced by the splanchnic bed is excreted in the urine [9].

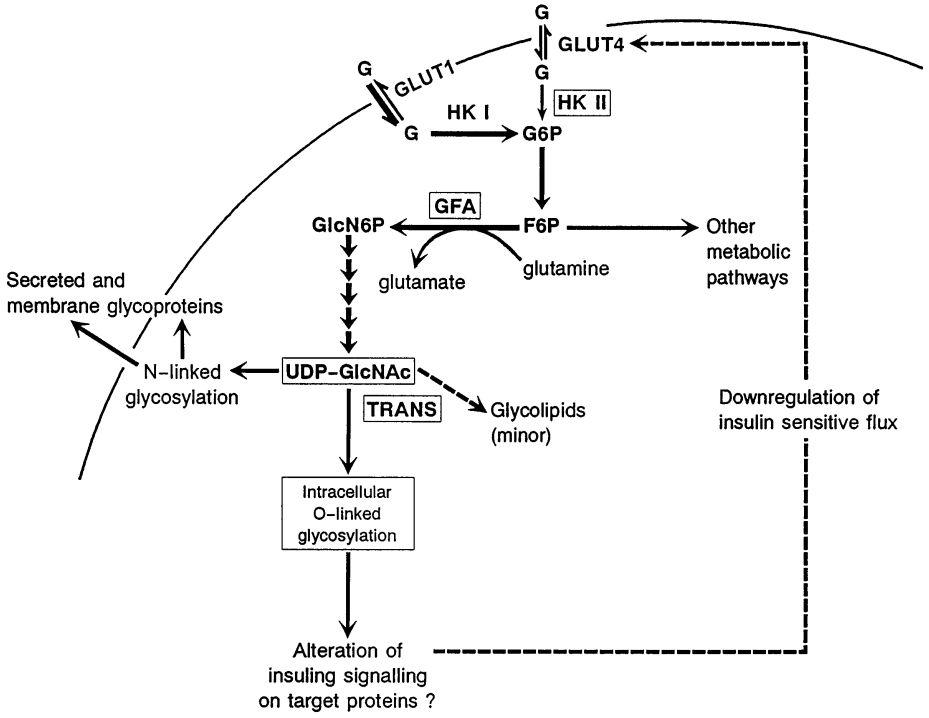

Fig. 1. An overview of glucose metabolism via the hexosamine pathway in skeletal muscle. Under hyperglycaemic conditions, glucose (G) is transported in excessive amounts (thick arrow) [5] via the non-insulin-sensitive glucose transporter (GLUT1), phosphorylated via the non-insulin-sensitive hexokinase isoform (HKI). This results in increased glucose flux via the hexosamine pathway. GFA catalyses the first and rate-limiting reaction of the hexosamine pathway, the reaction of fructose 6-phosphate (F6P) with glutamine to form glutamate and glucosamine 6-phosphate (GlcN6P). GlcN6P is converted via a series of non-rate-limiting reactions to uridine-diphospho-N-acetyl-glucosamine (UDP-GlcNAc), which can then either be incorporated to serine and threonine residues on intracellular proteins in a reaction catalysed by a uridine diphospho-N-acetylglucosamine:polypeptide β-N-acetylglucosaminyltransferase (TRANS) [31] (O-linked glycosylation), or linked to asparagine residues on secretory and membrane glycoproteins by other transferases [28] (N-linked glycosylation). Under hyperglycaemic normo- or hyperinsulinaemic conditions, levels of hexosamine metabolites [24] and GFA [26, 32] are increased implying increased flux through the pathway

Fasting hyperglycaemia is an important determinant of insulin resistance in IDDM and NIDDM

In patients with IDDM, insulin sensitivity is normal if glycaemic control is normalized [12]. The degree of peripheral insulin resistance in both IDDM [12] and NIDDM [13] is inversely related to the magnitude of fasting hyperglycaemia and the glycated haemoglobin concentration. Even in populations such as the Pima Indians [13] and Mexican Americans (unpublished data), in which insulin resistance is severe and possibly genetic, fasting glycaemia is the most important determinant of insulin sensitivity in patients with NIDDM. The ability of hyperglycaemia to induce insulin resistance has been shown directly in patients with IDDM. Elevation of plasma glucose concentrations for 24 h, to pathophysiologically relevant glucose concentrations (14–20 mmol/l) significantly decreases glucose uptake [14, 15]. The glucose-induced insulin resistance is localized in skeletal muscle, where defects in glucose extraction rather than delivery limit cellular glucose availability. This extraction defect is observed both in patients with NIDDM [16] and IDDM [14, 17, 18], when glucose uptake is measured under normoglycaemic hyperinsulinaemic conditions using physiological insulin concentrations [14, 19]. If, however, glucose uptake is measured under hyperglycaemic hyperinsulinaemic conditions, i.e. simulating everyday life, glucose uptake is normal in both patients with IDDM [18] and NIDDM [9]. This normality is consistent with the observed normal absolute glucose fluxes postprandially in such patients (see above) and has even been demonstrated in muscle strips isolated from patients with NIDDM [20].

Hyperglycaemia-induced insulin resistance is the consequence of overactivity of the hexosamine pathway

Hexosamine metabolism as a glucose sensor. The remarkable ability of insulin-sensitive tissues to maintain their rate of glucose uptake similar to that in normal individuals, despite a hyperglycaemic milieu, sug-

gests that cells sense and adapt to alterations in glucose flux. The existence of a 'glucose sensing pathway' remained hypothetical until studies performed in primary cultures of rat adipocytes suggested that the hexosamine pathway may serve such a purpose [21] (Fig. 1). This pathway metabolizes only a small fraction of glucose in insulin-sensitive tissues but its activation is both sufficient and necessary for glucose-induced desensitization of glucose transport in adipocytes [21]. The enzyme glutamine: fructose 6-phosphate amidotransferase (GFA) catalyses the first and rate-limiting reaction of the hexosamine pathway [22] (Fig. 1). Transgenic mice overexpressing GFA in skeletal muscle exhibit severe insulin resistance [23]. In rats, acute hyperglycaemia increases muscle hexosamine concentrations in a plasma glucose concentration-dependent manner [24]. Activation of the pathway via infusion of glucosamine, which bypasses the reaction catalysed by GFA, induces insulin resistance in normal but not diabetic, moderately insulin-deficient rats, suggesting that an overactive hexosamine pathway may mediate insulin resistance in these rats [25]. When measured in skeletal muscle biopsy specimens of patients with NIDDM, GFA is increased in proportion to the HbA_{1c} concentration [26]. The end-product of the hexosamine pathway, UDP-N-acetylglucosamine, is covalently attached to serine and threonine residues on cytosolic and nuclear proteins (intracellular O-linked glycosylation) [27], or to asparagine residues on secreted and surface proteins (N-linked glycosylation) [28]. As O-linked glycosylation appears to behave in a dynamic fashion in cells analogous to phosphorylation/dephosphorylation [29], it is a potential, but as yet an unproven candidate for mediating inhibitory effects of increased glucose flux on targets of insulin action such as translocation of GLUT4 [30].

Conclusions

Despite hyperglycaemia, which promotes glucose uptake, patients with IDDM and NIDDM are able to maintain the absolute glucose flux to insulin-sensitive tissues remarkably normal under everyday conditions of hyperglycaemia. This normality of glucose flux is achieved at the expense of insulin resistance. Recent data support the idea that the hexosamine pathway acts as a cellular sensor of glucose flux. Its activation by hyperglycaemia provides a feasible mechanism for maintenance of normal glucose flux in tissues such as skeletal muscle – one of the few tissues spared from long-term diabetic complications. Isolation of intracellular O-linked glycosylated proteins and characterization of their possible role in the regulation of insulin signalling is, however, needed to fully understand the molecular link between glucose flux and insulin action.

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