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Review

Acute and chronic effects of hyperglycaemia on glucose metabolism

H. Yki-Järvinen

Second Department of Medicine, Helsinki University, Helsinki, Finland

Summary. In normal man, several hormonal and metabolic adjustments allow the maintenance of the blood glucose concentration within narrow limits. Hyperglycaemia participates in this regulation via stimulation of glucose disposal and inhibition of glucose production. The effects are mediated, in addition to changes in insulin and glucagon secretion, by the mass-action effect of glucose. In both Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetic patients, hyperglycaemia, by mass-action abnormally elevates the basal glucose utilization rate but compensates for reduced postprandial insulin-stimulated glucose disposal. When exposed to chronic hyperglycaemia, the body tissues seem to protect themselves, at least partly, against excessive glucose utilization. These protective mechanisms include both a reduction in insulin stimulated glucose disposal and insulin secretion. Chronic hyperglycaemia may also reduce non-insulin-dependent glucose utilization, at least in rats. In Type 1 diabetic patients with normal peripheral insulin concentrations, chronic hyperglycaemia per se could be a major cause of insulin resistance. In Type 2 diabetic patients, insulin resistance is often already present before the development of overt fasting hyperglycaemia. At the diabetic stage, hyperglycaemia could, however, maintain a self-perpetuating cycle, where the deleterious effects of high glucose concentrations on insulin action and secretion cause further deterioration of glycaemic control. The biochemical basis for hyperglycaemia-induced insulin resistance is still far from clear, but could involve changes in the glucose transporter number and gene expression.

Key words: Glucose, insulin, diabetes, glucose transport, insulin resistance.

In 1985, in this journal, Unger and Grundy proposed that chronic hyperglycaemia could be an inducer as well as a consequence of both impaired Beta cell function and insulin resistance in diabetic patients [1]. In recent years, this hypothesis has been experimentally tested in studies carried out both in vivo and in vitro. In contrast to the inhibitory effects of chronic hyperglycaemia on both glucose utilization and insulin secretion, acute hyperglycaemia stimulates, by the mass-action effect of glucose, both of these processes. Stimulation of glucose utilization by hyperglycaemia has important implications with respect to the understanding of mechanisms maintaining hyperglycaemia in diabetic patients. The ensuing discussion is focussed on reviewing our present knowledge of the effects of acute and chronic hyperglycaemia on glucose metabolism. The clinical significance of these data for the treatment of Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetic patients will also be addressed.

Acute effects of hyperglycaemia on glucose metabolism

Glucose utilization

In normal subjects, the effect of hyperglycaemia per se on glucose utilization can be studied, in the virtual absence of insulin and at different insulin concentrations, by employing simultaneous infusions of glucose, insulin, and somatostatin. Somatostatin blocks endogenous insulin release as well as growth hormone and glucagon secretion [2]. When measured during inhibition of endogenous insulin release by somatostatin, whole body glucose utilization is stimulated in a glucose-concentration dependent manner [3, 4] both in the absence and presence of insulin (Fig. 1). Within the physiological range of insulin concentrations, doubling the plasma glucose concentration will approximately double glucose utilization (Fig. 1). The ability of glucose to promote glucose utilization depends on the insulin concentration; an increase in the plasma glucose concentration from 5 to 9 mmol/l at insulin concentrations of 9 (fasting), 50 (postprandial), 160 and 1800 mU/l will increase glucose utilization by ~1.8, ~2.7, ~6.6 and ~11.5 mg/kg fat free mass · min in normal subjects [3]. The glucose-induced increases in glucose utilization are quantitatively significant compared to those induced by insulin alone under normoglycaemic conditions (Fig. 1). The increments in glucose utilization in response to acute increments in plasma glucose appear normal in Type 1 diabetic patients, in whom the insulin-induced increase in glucose utilization is reduced [5]. The normal glucose-mediated glucose uptake in these patients has been interpreted to suggest normal function of glucose transporters with the decrease in insulin-mediated glucose uptake being due to a reduced total number of glu-

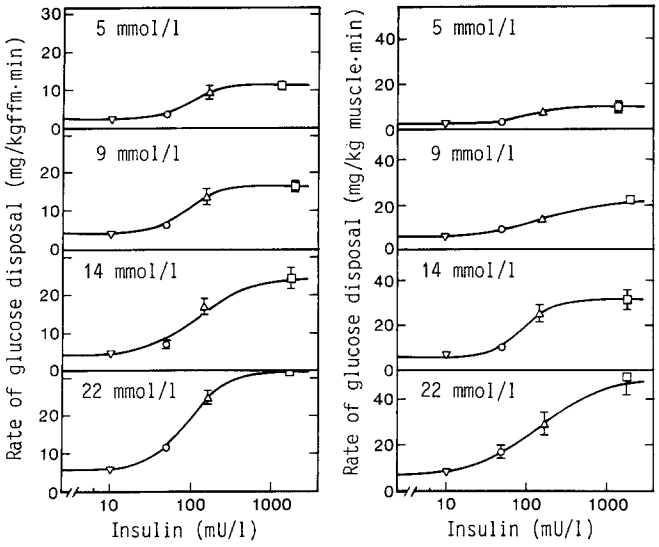

Fig. 1. Effect of glucose and insulin on whole body (left) and forearm glucose uptake (right) in normal subjects [3]

cose transporters [5], impaired mobilization of transporters from an intracellular pool to the cell surface membrane [6], or perhaps to impaired transporter activation in the plasma membrane of the cell [7].

Under intravenously maintained normoglycaemic hyperinsulinaemic conditions, muscle tissue is responsible for most (60–80%) of the glucose utilization [3, 8]. In response to hyperglycaemia, glucose uptake in muscle increases in a similar dose-dependent fashion as at the whole body level (Fig. 1). Hyperglycaemia induced by intravenous glucose is also capable of enhancing splanchnic glucose uptake in man [9, 10]. This increase is explained by increased delivery of glucose to the splanchnic area rather than an increase in the intrinsic ability of the splanchnic bed to retain glucose [10]. It has been reported that insulin is required for stimulation of splanchnic glucose uptake by hyperglycaemia and that net splanchnic glucose uptake during intravenously induced hyperglycaemia accounts for only ~5% of total glucose uptake by all tissues in the body [9, 10].

After hyperglycaemia induced by oral glucose, net splanchnic glucose uptake is ~6-fold higher than after intravenous glucose, when peripheral glucose concentrations are maintained identical [10]. This difference is not explained by differences in the portal or peripheral insulin concentrations, but may be related to activation the autonomic nervous system, and/or to a greater portal-arterial glucose concentration difference during oral than intravenous glucose [11].

Hyperglycaemia stimulates both oxidative and non-oxidative glucose disposal in normal subjects [12]. When compared at matched rates of glucose utilization, induced either by hyperinsulinaemia or hyperglycaemia, glucose is less potent than insulin in stimulating glucose oxidation under physiological conditions [12]. The superiority of insulin in promoting glucose oxidation seems to be related to its antilipolytic effect [12]. Even a small increment in serum insulin promptly suppresses plasma non-esterified fatty acids and lipid oxidation and this can increase glucose oxidation [13]. On the other hand, hyperglycaemia probably has no antilipolytic effect in vivo [12]. At higher matched rates of glucose disposal (e.g. insulin 50 mU/l and glucose 24 mmol/l vs insulin 1700 mU/l and glucose 5 mmol/l), glucose oxidation becomes entirely dependent on intracellular glucose availability and then hyperglycaemia and hyperinsulinaemia become equipotent stimulators of glucose oxidation [12].

Intracellularly, the acute stimulatory effect of hyperglycaemia on muscle glucose utilization through oxidative and non-oxidative pathways could be explained by simple mass-action. In contrast to insulin, which stimulates muscle glucose oxidation and glycogen synthesis via changes in the phosphorylation state of key regulatory enzymes (e.g. dephosphorylation of glycogen synthase and pyruvate dehydrogenase, [14, 15]), hyperglycaemia increases muscle glycogen content without dephosphorylation of glycogen synthase in humans [14, 16]. In the perfused rat liver, however, hyperglycaemia does stimulate glycogen synthase activity and inhibit glycogen phosphorylase activity, independent of, and even in the absence of insulin [17].

Non-oxidative glycolysis, as determined from net muscle lactate release, is not stimulated by hyperglycaemia [18–20]. However, the plasma lactate concentration is highly correlated with the rate of whole body glucose disposal under conditions where hepatic glucose production is suppressed, and can be increased by hyperglycaemia, independent of insulin [18]. The most plausible explanation for these data is that hyperglycaemia stimulates non-oxidative glycolysis in tissues other than muscle [18].

Glucose production

Hyperglycaemia, independent of insulin and glucagon, inhibits hepatic glucose production [3, 9]. Half-maximal inhibition of hepatic glucose production is achieved at a glucose concentration of 9 mmol/l in normal subjects [3]. This glucose concentration could be an underestimation due to problems inherent to isotopic measurement of glucose production [21, 22]. Whether the sensitivity of glycogenolysis and gluconeogenesis to inhibition by hyperglycaemia are similar is presently unclear. In the study of Bell et al. [23], the rate of glucose recycling (a qualitative index of gluconeogenesis), remained unchanged in response to an increase in plasma glucose from 5.3 to 9.7 mmol/l [23]. The rate of glucose recycling at the 9.7 mmol/l glucose concentration was similar to the total rate of hepatic glucose production suggesting that hyperglycaemia was more effective in suppressing glycogenolysis than gluconeogenesis [23]. The rate of the futile cycle at the level of glucose/glucose-6-phosphate is not altered by hyperglycaemia [23, 24].

Consequences of the acute stimulatory effect of hyperglycaemia on glucose disposal in Type 1 and Type 2 diabetic patients

Increased glucose utilization after an overnight fast

The fasting plasma glucose concentration is directly proportional to the rate of endogenous glucose production in both Type 1 and Type 2 diabetic patients [25, 26]. As a

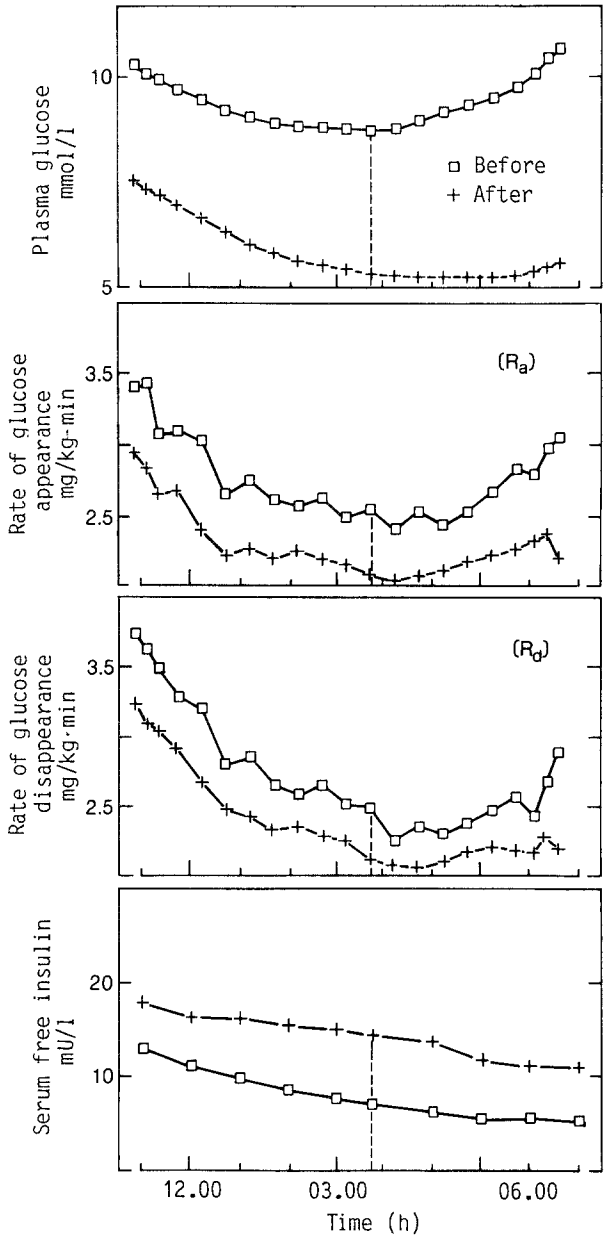

Fig. 2. Example of the mass-action effect of glucose during treatment of patients with Type 2 (non-insulin-dependent) diabetes with insulin. Plasma glucose and serum free insulin concentrations, and rates of glucose appearance and disappearance were measured before (□) and after (+) treatment of Type 2 diabetic patients with evening insulin therapy [28]. Despite a significant increase in the serum free insulin concentration (bottom panel), the rate of glucose disappearance decreased significantly as a consequence of the decrease in plasma glucose caused by the decrease in glucose glucose production

consequence of the mass-action effect of glucose, fasting glycaemia also is positively correlated with the rate of glucose utilization [25, 26]. The rate of basal glucose utilization is increased in both types of diabetes [25, 27]. The effect of evening insulin therapy on glucose production and utilization in Type 2 diabetic patients demonstrates the practical consequence of the glucose mass-action effect. Although insulin stimulates glucose utilization, the rate of overnight glucose utilization is decreased rather than increased by insulin therapy because inhibition of glucose production decreases the plasma glucose concentration, and the rate of glucose utilization (Fig. 2, [28]). Thus, the inhibitory effect of reduced glucose mass-action on glucose utilization overrides the stimulatory effect of insulin on glucose utilization. These data also imply that fasting hyperglycaemia is the consequence of increased hepatic glucose production rather than impaired glucose utilization. Therefore, therapeutic measures aimed at reducing fasting hyperglycaemia should inhibit hepatic glucose production rather than further increase glucose utilization.

Although in the basal state, the absolute rate of glucose utilization is increased, an impairment in the mass-action effect of glucose could contribute to maintenance of hyperglycaemia in diabetic patients [29, 30]. However, in this context it is important to remember that at low insulin concentrations, 50–60% of glucose is utilized at a fixed rate by the brain [31]. Since the brain does not increase its glucose uptake in response to hyperglycaemia [32], whole body glucose clearance i. e. the rate of glucose utilization divided by the plasma glucose concentration will decrease as the plasma glucose concentration increases [3, 4, 27].

Hyperglycaemia compensates for insulin resistance under postprandial conditions

When measured under normoglycaemic conditions using the insulin clamp technique [33], the ability of insulin to increase total, oxidative and non-oxidative glucose disposal is reduced in both Type 1 [25] and Type 2 [26] diabetic patients. However, if the rate of glucose disposal is determined in Type 1 [13] or Type 2 [34] diabetic patients at glucose concentrations characterizing these patients during their everyday life, glucose utilization is normal. Hyperglycaemia also normalizes the flux through oxidative and non-oxidative pathways in both Type 1 [16] and Type 2 [34] diabetic patients. In Type 1 diabetic patients, normalization of muscle glucose uptake by hyperglycaemia corrects the defect in muscle glycogen synthesis found in these patients under normoglycaemic conditions [16]. This occurs without a change in muscle free glucose or glucose-6-phosphate concentrations indicating that hyperglycaemia overcomes by mass-action a rate-limiting defect at the level of glucose transport [16].

Total body and muscle glucose disposal rates also are normal in Type 2 diabetic patients during an oral glucose tolerance test [33], and in Type 1 diabetic patients after ingestion of a mixed meal [34] and oral glucose [35–37]. In the latter studies, postprandial hyperglycaemia resulted from impaired suppression of hepatic glucose production [35–37]. These studies indicate that hyperglycaemia and the enhanced glucose utilization by glucose mass-action compensate for the reduction in the efficiency of glucose disposal due to insulin resistance in hyperglycaemic Type 1 and Type 2 diabetic patients.

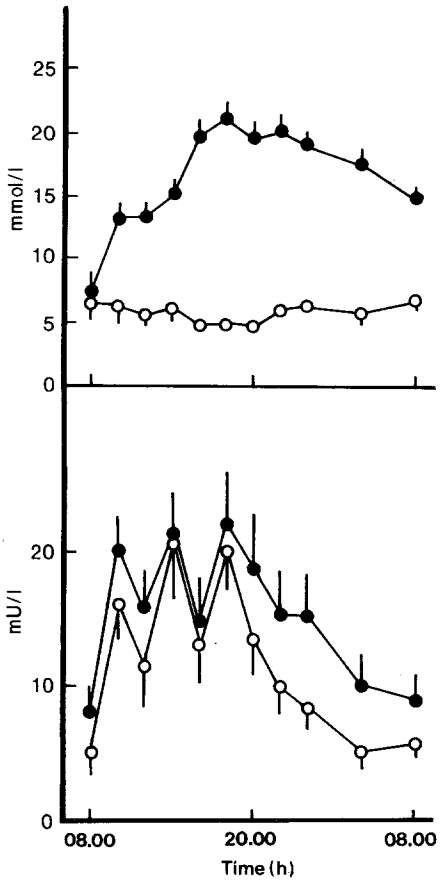

Fig. 3. Plasma glucose (top panel) and free insulin concentrations (bottom panel) during induction of hyperglycaemia by an intravenous glucose infusion in 10 Type 1 diabetic patients treated with continuous subcutaneous insulin infusion therapy. During the control day, the patients received identical diets and insulin doses as during the hyperglycaemic day, with being infused instead of glucose [3]

Chronic effects of hyperglycaemia on glucose metabolism

In 1987, evidence was first presented for the ability of hyperglycaemia to induce insulin resistance in Type 1 diabetic patients [38]. Similar conclusions were reached from studies in partially pancreatectomized rats [39].

Type 1 diabetic patients

Insulin-stimulated glucose uptake was measured in 10 Type 1 diabetic patients treated with continuous subcutanous insulin infusion on two occasions, after 24 h of hyperglycaemia induced by an intravenous glucose infusion (mean diurnal glucose 16 mmol/l) and after 24 h of normoglycaemia (6 mmol/l, [38], Fig. 3). After 24 h of hyperglycaemia, the rate of insulin-stimulated glucose uptake was consistently lower than after the normoglycaemic period demonstrating that short-term hyperglycaemia can induce insulin resistance in humans ([38], Fig. 4).

Diabetic rats

In the study by Rossetti et al. [39] diabetes was induced in rats by removing 90% of the pancreas. The diabetic state was associated with a 30% reduction in insulin-mediated glucose uptake. Hyperglycaemia was treated (without altering the circulating insulin concentrations) by phlorizin, which inhibits glucose reabsorption by the proximal tubuli. Treatment with phlorizin normalized insulin sensitivity in the diabetic rats. The hyperglycaemia induced insulin resistance seemed restricted to impaired stimulation of glucose uptake and did not include suppression of glucose production by insulin [39]. On the other hand, hepatic insulin resistance cannot be conclusively excluded, as insulin sensitivity was measured using an insulin dose which caused near-maximal suppression of glucose production.

Mechanisms of hyperglycaemia-induced insulin resistance

The exact biochemical mechanism by which chronic hyperglycaemia reduces glucose uptake is unclear. In vitro, pre-exposure of cultured rat skeletal muscle myocytes and myotubes [40, 41] and 3T3-L1 adipocytes [42] to high glucose concentrations, reduces 2-deoxyglucose uptake. The decrease in glucose uptake is due to a reduction in the maximal velocity rather than the affinity of the glucose transport system [40, 42]. Downregulation of the transport system in cultured 3T3-L1 fat cells can be induced, in addition to glucose, by methylglucose and mannose, which are taken up in competition with 2-deoxyglucose but not with the non-competing hexoses galactose and fructose [42]. These data suggest that transport but not further metabolism is required for downregulation of the glucose transport system by hoxoses in cultured fat cells [42]. High glucose concentrations do not change muscle ATP and free intracellular glucose concentrations [40, 42]. The glucose-indiced downregulation appears to be restricted to the glucose transport system, at least α-aminobutyric acid uptake is not altered by glucose [40].

Over the past 5 years, major advances have been made in understanding the molecular basis for cellular glucose transport [43]. At least four glucose transporter-like proteins have been identified by cDNA cloning techniques. The effect of hyperglycaemia on the glucose transporter gene expression has been studied using cDNA probes recognizing the mRNA of the adipocyte/muscle and the HepG2/brain type glucose transporter. The adipocyte/muscle glucose transporter mRNA is expressed exclusively in insulin-sensitive tissues (muscle, adipose tissue), while the HepG2/brain type glucose transporter is found both in insulin-dependent and insulin-independent tissues [43].

In cultures of the rat brain glial cells, glucose starvation induces increases in glucose transport, glucose transporter protein and the mRNA for the rat brain glucose transporter [44]. Opposite changes are observed when glucose starved cells are exposed to glucose [44]. Chronic hyperglycaemia has also been shown to decrease the glucose transport capacity of the rat blood-brain barrier [45]. In cultured rat skeletal muscle cells, exposure to high glu-

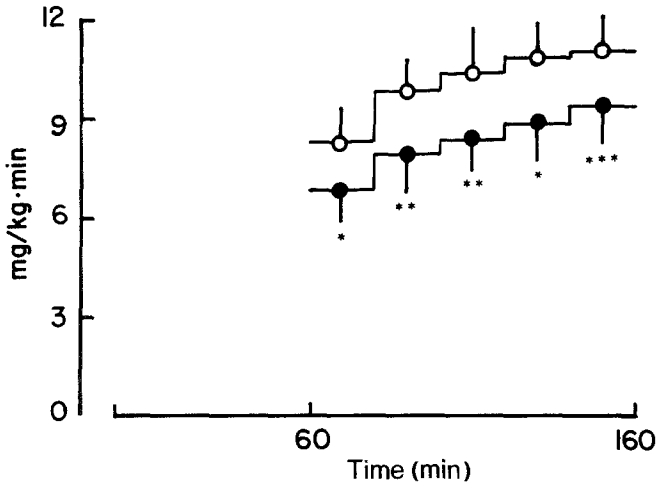

Fig. 4. Rates of glucose metabolism, measured during maintenance of similar glucose and insulin concentrations, after 24 h of hyperglycaemia (●) and after 24 h of normoglycaemia (○, Fig. 3) in 10 Type 1 diabetic patients. The rate of glucose metabolism was significantly lower after hyper- than normoglycaemia, demonstrating induction of insulin resistance by a 24 h exposure to hyperglycaemia

cose concentrations decreases both glucose uptake, the transporter protein and the mRNA for the rat brain glucose transporter [41]. The increase in glucose transport by insulin is also lower in cells cultured in the presence rather than in the absence of glucose [41]. Preliminary data would suggest that hyperglycaemia does not change the mRNA concentration for the adipose/muscle glucose transporter in cultured rat skeletal muscle cells or 3T3-L1 adipocytes [41].

Contribution of hyperglycaemia-induced insulin resistance to insulin resistance in Type 1 and Type 2 diabetes

Type 1 diabetic patients

Before directly proving that hyperglycaemia can induce insulin resistance in Type 1 diabetic patients, several lines of indirect evidence had suggested this could be the case. First, in both a small ($n = 18$, [46]), and a larger ($n = 53$, [25]) group of insulin-treated C-peptide negative Type 1 diabetic patients, an inverse relationship between long-term glycaemic control as measured by glycosylated haemoglobin (HbA_1) and insulin sensitivity was observed. Since mean peripheral insulin concentrations in insulin-treated Type 1 diabetic patients are usually not lower than those in non-diabetic subjects [47], peripheral hypoinsulinaemia cannot explain reduced insulin-stimulated glucose uptake by peripheral tissues. In support of this, the mean insulin dose/body weight, insulin antibodies, or residual endogenous insulin secretion did not correlate with insulin action in insulin-treated Type 1 diabetic patients [25]. In addition, previous studies in Type 1 diabetic patients demonstrated that glycaemic control and insulin sensitivity could be improved by continuous subcutaneous insulin infusion therapy without having to increase the total insulin dose [48, 49]. Combining these indirect data and the direct demonstration of the ability of hyperglycaemia to impair insulin action, it can be postulated that hyperglycaemia per se is a major cause of insulin resistance in Type 1 diabetic patients.

As no portal/peripheral insulin gradient exists in Type 1 diabetic patients, the liver is underinsulinized compared to normal subjects, and therefore overproduces glucose [49]. From these data a pathogenic scheme for insulin resistance in these patients can be postulated: fasting and postprandial portal hypoinsulinization leads to overproduction of glucose by the liver, chronic hyperglycaemia and insulin resistance.

Type 2 diabetic patients

Recent prospective [50–53] and crossectional [54, 55] studies have provided evidence that hyperinsulinaemia and insulin resistance precede and predict the subsequent development of Type 2 diabetes. In these studies the defect in insulin action appears to be detectable already in subjects with normal glucose tolerance [50–55]. Therefore, chronic hyperglycaemia is unlikely to be the cause of the initial insulin resistance. Once diabetes has developed, the progressive increase in fasting plasma glucose concentrations seems to be better explained by deterioration of insulin secretion than by worsening of insulin resistance [50]. The progressive deterioration of insulin secretion could be both a cause and a consequence of chronic hyperglycaemia [50, 56]. It has also been proposed that the progression of glucose tolerance from impaired to diabetic could be due to effects of mild chronic hyperglycaemia on beta-cell function [50, 56]. This proposal is, however, presently far from proven and awaits localization of the primary cause of Type 2 diabetes.

Regarding the significance of chronic hyperglycaemia on glucose metabolism in established Type 2 diabetes, one could intuitively assume that it impairs glycaemic control by worsening the pre-existing (inherited?, [57]) insulin resistance. At present, only indirect evidence exists to support this proposal. Several modes of diabetic therapy, including insulin, oral agents, weight loss, and exercise improve both glycaemic control, insulin secretion and insulin sensitivity. However, as all of these treatments may improve insulin sensitivity also by mechanisms not mediated via changes in the blood glucose concentration [26], it is unclear to what extent insulin sensitivity is improved by reduction of chronic hyperglycaemia per se.

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H. Yki-Järvinen, M.D.
Second Department of Medicine
Helsinki University
Haartmaninkatu 4
SF-00290 Helsinki
Finland