Effects of fructose on hepatic glucose metabolism

Owen P. McGuinness and Alan D. Cherrington

Purpose of review

The liver plays an important role in glucose tolerance. A number of studies have suggested fructose improves glucose tolerance especially in insulin resistant settings. This review summarizes the recent work suggesting that fructose enhances glucose tolerance by augmenting liver glucose uptake. This increase may be mediated by the translocation and activation of hepatic glucokinase.

Recent findings

Catalytic quantities of fructose ($<10\%$ of total carbohydrate flux) enhance liver glucose uptake in a dose dependent manner. The primary fate of the glucose is glycogen synthesis. The ability of fructose to augment liver glucose uptake is not impaired by the presence of marked insulin resistance such as in type 2 diabetes or infection. In addition, it is able to further enhance liver glucose uptake in the normal adapted setting of total parenteral nutrition and reverse the infected-induced decrease in liver glucose uptake. Studies also demonstrate that the beneficial effects of fructose on liver glucose uptake during chronic nutritional support do not persist.

Summary

Fructose is a potent acute regulator of liver glucose uptake and glycogen synthesis. Inclusion of catalytic quantities of fructose in a carbohydrate meal improves glucose tolerance. This improvement is primarily mediated by the activation of hepatic glucokinase and consequent facilitation of liver glucose uptake. The improvement in glucose tolerance is most evident in insulin resistant settings (e.g. Type 2 diabetes and infection). The beneficial effect of fructose on hepatic glucose disposal, however, does not persist if fructose is given continuously such as in total parenteral nutrition.

Keywords

fructose, metabolism, hepatic glucokinase, glycogen synthesis

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Abbreviations

GKRP	glucokinase regulatory protein
TPN	total parenteral nutrition
UDPG	Uridine diphosphate glucose

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Introduction

Fructose is the sweetest of the simple sugars. In recent years the contribution of fructose to dietary carbohydrate has increased as high fructose corn syrup has replaced sucrose as a sweetener. The metabolism of fructose is markedly different from that of glucose, with the liver playing a significantly larger role in its metabolism. Fructose can have very diverse effects depending upon the quantity ingested. Not surprisingly, in the acute setting, when fructose replaces glucose as the sole carbohydrate source, the post prandial glucose response is decreased; this is considered a benefit in settings of glucose intolerance. Fructose has some negative effects. When large quantities of fructose are administered, it can also serve as a potent substrate for gluconeogenesis and lipogenesis and it can elevate uric acid levels, all of which have been demonstrated to have long-term detrimental effects. In addition, individuals who are suspected of having hereditary fructose intolerance should avoid fructose [1,2]. Recent work, however, suggests that if very low doses (i.e. catalytic) of fructose are added to a glucose containing meal, glucose tolerance is improved. Fructose is thought to mediate this effect by activating liver glucokinase resulting in increased glucose phosphorylation and glycogen synthesis. It is this catalytic effect of fructose that will be the focus of this update.

Determinants of liver glucose uptake

The liver plays a central role in maintaining glucose homeostasis because of its ability to rapidly switch from a glucose producer to a glucose consumer. In the fasted state the liver is the main endogenous source of glucose, producing around 2 mg/kg/min. After an overnight fast the glucose carbon is derived from both glycogenolysis and gluconeogenesis. Following an oral glucose load the liver rapidly switches to a glucose consumer, reaching rates of uptake as high as 6 mg/kg/min. Consequently, the liver removes approximately one-third of an oral carbohydrate load. The disposal of the remaining two-thirds of the carbohydrate load is equally distributed between insulin dependent (muscle, adipose tissue) and insulin independent (brain, red blood cells) tissues. A failure of the liver to rapidly and robustly switch from a glucose producer to a glucose consumer contributes to the glucose intolerance of patients with type 2 diabetes [3].

The primary determinants of liver glucose uptake are the glucose and insulin concentrations and the route of glucose delivery (Fig. 1). Hyperglycemia (200 mg/dl) or physiologic hyperinsulinemia (20–40 μU/ml) alone,

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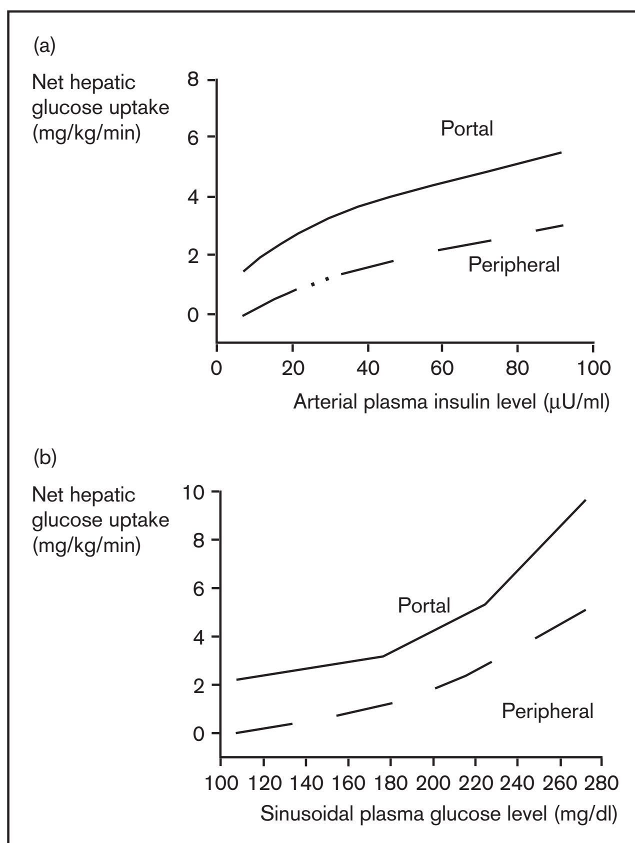
Figure 1. The relationship between insulin and glucose levels and net hepatic glucose uptake



The relationship between arterial insulin levels and net hepatic glucose uptake (a) in the presence of hyperglycemia (220 mg/dl) in chronically catheterized conscious dogs. The relationship between hepatic sinusoidal glucose levels and net hepatic glucose uptake (b) in the presence of fourfold basal insulin in chronically catheterized conscious dogs. Adapted from Galassetti *et al.* [5] and Myers *et al.* [6,7].

while able to suppress hepatic glucose production, are unable to convert the liver to a significant glucose consumer [4]. Only with pharmacologic insulin concentrations ($>1000\ \mu$U/ml) can the liver become a significant glucose consumer in the presence of euglycemia. The combination of hyperglycemia (~ 200 mg/dl) and hyperinsulinemia can, however, induce substantial liver glucose uptake. In the presence of hyperglycemia the liver is very responsive to changes in insulin levels (Fig. 1a). The liver is also responsive to changes in glucose levels in the presence of physiologic hyperinsulinemia (three- to fourfold basal). However, the combined effects of hyperglycemia and hyperinsulinemia that accompany a carbohydrate meal alone cannot explain the substantial contribution of the liver to the disposal of an oral glucose load. If glucose is given orally, liver glucose uptake is greater than if the glucose is given into a peripheral vein. This route dependent augmentation of liver glucose uptake can be recapitulated by circumventing the intestine and delivering the glucose directly into the portal vein. Consequently, the route dependent augmentation of liver glucose uptake has been termed the 'portal signal'. The augmentation of liver glucose uptake by portal delivery of glucose occurs over a wide range of physiologic glucose and insulin levels (Fig. 1) [5–7]. It is a rapid response that is dependent upon the presence of insulin. In addition, it decreases insulin dependent peripheral glucose uptake thus further augmenting the important role of the liver in the disposal of an oral carbohydrate load. The mechanism for the route dependent increase in liver glucose uptake is unclear. However, hepatic innervation is required [8]. Thus, the combined effects of hyperglycemia, hyperinsulinemia and the portal signal can explain the rapid and substantial augmentation of liver glucose uptake following an oral glucose load.

Metabolic fate of glucose

Interestingly, while the magnitude of liver glucose uptake is dependent on the route of glucose delivery, the metabolic fate of the glucose within the liver is not. In the absence or presence of the portal signal the major fate of the glucose removed by the liver is glycogen deposition. The facilitation of glycogen deposition requires the redirection of glucose carbon flux at three metabolic steps: hepatic glucose phosphorylation/dephosphorylation (glucokinase and glucose 6 phosphatase), glycogen synthesis/breakdown (glycogen synthase and phosphorylase), and gluconeogenesis/glycolysis (pyruvate kinase, phosphofructokinase and phosphoenolpyruvate carboxykinase). The key metabolic intermediate is glucose 6 phosphate. The uptake of gluconeogenic precursors by the liver and their subsequent conversion to glucose 6 phosphate is not significantly suppressed during a carbohydrate meal. The majority of the gluconeogenic carbon is diverted to glycogen synthesis rather than being released by the liver. While the liver has the capacity to be glycolytic and release significant quantities of lactate, less than 20% of the glucose carbon taken up by the liver is normally diverted to lactate. Thus, on balance, there is a net movement of gluconeogenic precursors into the glucose 6 phosphate pool during a mixed meal. The diversion of gluconeogenic precursors from glucose 6 phosphate to glycogen is facilitated by the activation of glycogen synthase and inhibition of glycogen phosphorylase. This activation is facilitated by the accompanying rise in insulin and glucose 6 phosphate, a potent allosteric activator of glycogen synthase. Yet activation of glycogen synthase alone would not lead to substantial rates of glycogen synthesis without a source of glucose 6 phosphate in addition to gluconeogenic precursors.

Facilitation of hepatic glucose phosphorylation plays an essential role in the augmentation of hepatic glucose

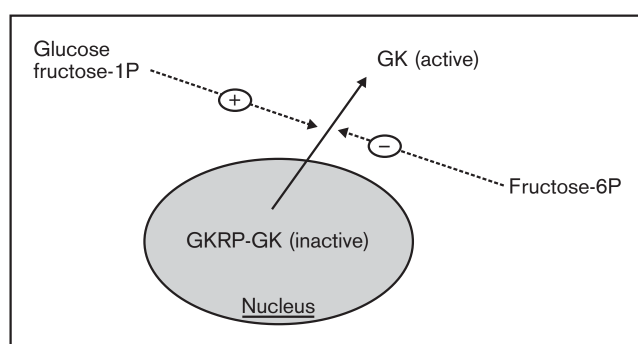
uptake and glycogen synthesis during a meal. In the liver glucose entry is facilitated by GLUT-2, which is not thought to be acutely regulated. Glucose phosphorylation by hexokinase IV (i.e. glucokinase), however, is regulated. Glucokinase is a low-affinity (Km = ~7–8 mM) high-capacity hexokinase. It is a unique member of the hexokinase family. In contrast to other hexokinases, the product glucose 6 phosphate does not inhibit glucokinase in the physiologic range of glucose 6 phosphate concentrations. Glucokinase activity is regulated by modulating both the quantity and intracellular localization of the enzyme. The expression of glucokinase increases during the transition of individuals from a high-fat diet seen during weaning to a carbohydrate rich diet [9]. The expression of glucokinase is facilitated by insulin and inhibited by glucagon. The intracellular localization of glucokinase is modulated by its association with glucokinase regulatory protein (GKRP), which is in molar excess and is located in the nucleus (Fig. 2). When bound to GKRP glucokinase is inactive [10]. A rise in intracellular glucose facilitates the dissociation of glucokinase from GKRP. Upon dissociation glucokinase enters the cytosolic compartment where it is active. In addition, fructose 6 phosphate and fructose 1 phosphate allosterically regulate this interaction. Increases in fructose 1 phosphate enhance the dissociation of the glucokinase/GKRP complex, while increases in fructose 6 phosphate favor association [11]. Since the activity of glucokinase is modulated both by the availability of glucose and the phosphate esters of fructose, dietary changes in the availability of fructose could modulate glucokinase activity.

Metabolism of fructose

The liver is the primary metabolic site of fructose disposal. Three factors contribute to this: (1) enzymes essential for the metabolism of fructose, fructokinase and triokinase, are highly expressed in the liver; (2) the liver is exposed to higher concentrations of orally administered fructose than other tissues; and (3) the high first pass extraction of fructose by the liver limits the availability of fructose for metabolism by peripheral tissues.

Hexokinases (including glucokinase) can phosphorylate fructose, however the presence of physiologic levels of glucose inhibit hexokinase phosphorylation of fructose. Yet the liver can efficiently remove fructose because of a highly efficient alternative pathway involving fructokinase. This enzyme is specific for fructose and is highly expressed in the liver. The product fructose 1 phosphate is rapidly split by aldolase to form glyceraldehyde and dihydroxyacetone phosphate. Glyceraldehyde is converted to glyceraldehyde-3 phosphate by triokinase. Thus, fructose is rapidly converted to two important intermediates in the glycolytic pathway (Fig. 3). Triokinase, like fructokinase, is expressed primarily in the liver and kidney [12]; there is limited expression in muscle and adipose tissue. Thus, while other tissues can metabolize significant quantities of fructose, nonphysiologic levels of fructose are required. Under normal circumstances the only source of fructose is of dietary origin. Fructose is rapidly absorbed by the intestine and enters the portal vein. Little if any of the fructose is actually metabolized by the intestine, except possibly at very low dietary intakes. As a consequence of the efficient intestinal absorption of fructose and the direct entry into the portal vein the levels of fructose in the portal vein are approximately four times the levels seen in an artery. The marked differences in portal vein and artery fructose levels result from the high first pass extraction of fructose by the liver (>50%). The combined effects of low enzymatic capacity of peripheral tissues to metabolize fructose and the high first pass extraction of fructose by the liver explains why more than 70% of dietary fructose is metabolized by the liver.

Figure 2. Control of glucokinase translocation

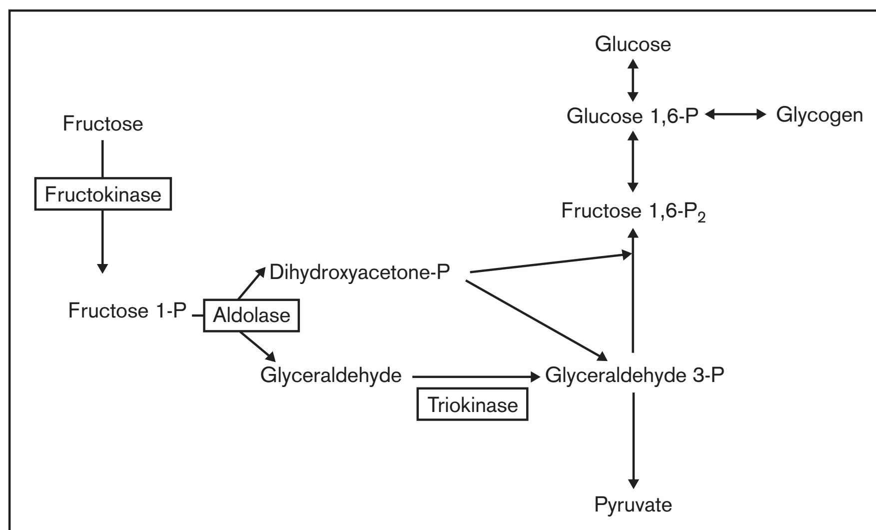


GKRP, glucokinase regulatory protein.

Physiologic response to fructose

The metabolic fate of fructose within the liver varies depending upon the metabolic status of the liver as well as the quantity of fructose that is administered. Fructose, when given intravenously at rates equal to or above endogenous glucose production, will induce hyperglycemia or impair peripheral glucose disposal. Very high fructose infusion rates into a peripheral vein (11 mg/kg/min) increase splanchnic glucose production and produce marked hyperglycemia in insulin-deficient diabetic patients [13]. In individuals without diabetes, hyperglycemia did not occur because of increases in insulin. However, both splanchnic lactate release and arterial lactate concentrations increased [13]. In a more recent study a lower dose of fructose (3 mg/kg/min) was infused into a peripheral vein in the presence of mild hyperglycemia and hyperinsulinemia. Endogenous glucose production failed to be appropriately suppressed despite higher insulin levels with fructose infusion. In

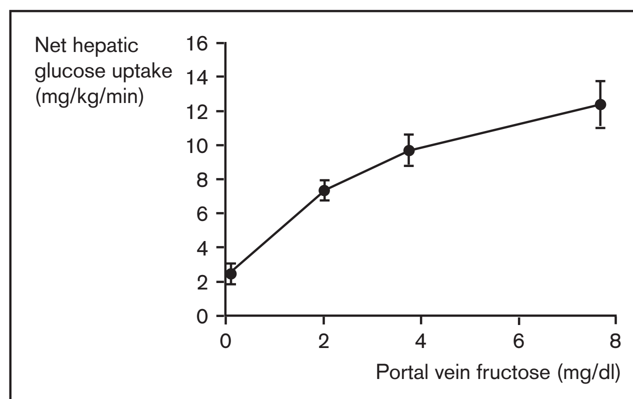
Figure 3. Metabolism of fructose



addition, the flux of glucose carbon through the UDPG pool was doubled, which is consistent with a diversion of the fructose carbon toward gluconeogenesis [14]. In rodents a similar effect of high doses of fructose was observed. Thus, when fructose supplies a significant quantity of the total carbohydrate, it can serve as a glucose precursor or compete with glucose as a substrate. Fructose is especially effective in inducing hyperglycemia if it is administered into a peripheral vein, thereby circumventing the liver where it could be metabolized by peripheral tissues.

Recent work suggests when small (i.e. catalytic) quantities of fructose are added to a glucose load, liver glucose uptake is amplified. In the chronically catheterized conscious dog, liver glucose uptake is very sensitive to fructose [15]. In the presence of somatostatin, hyperglycemia (200 mg/dl) of peripheral origin and 4 × basal insulin levels (30 μU/ml), liver glucose uptake is only 2.5 mg/kg/min. However, a stepwise increase in the infusion of fructose (0.3–0.6–1.2 mg/kg/min) into the portal vein increased arterial (1.7–3.4–6.8 mg/dl) and portal vein (6.3–11.7–23.8 mg/dl) fructose concentrations. Net hepatic glucose uptake increased in a dose dependent manner (Fig. 4). The increase in liver glucose uptake was paralleled by a rise in net hepatic lactate release (17%) and hepatic glycogen synthesis (70%). The majority of the glycogen was synthesized via the direct pathway. Thus in a very controlled setting of fixed hyperglycemia and hyperinsulinemia, catalytic quantities of fructose given into the portal vein markedly augment liver glucose uptake.

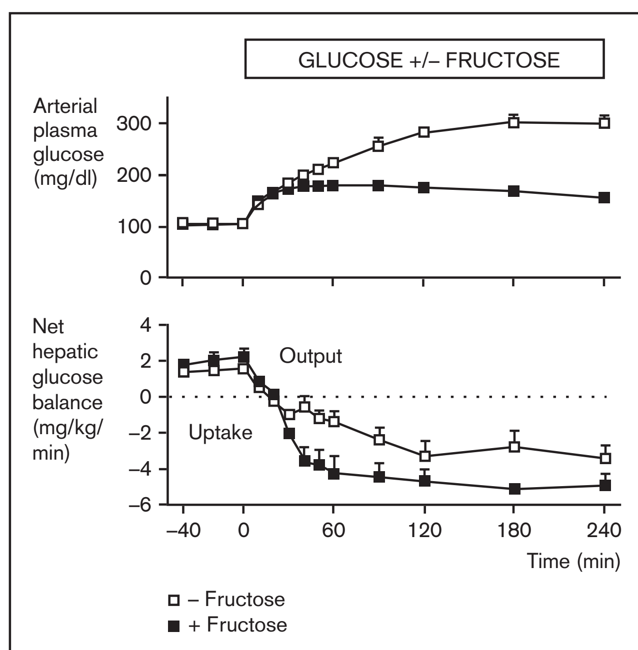
Figure 4. The dose–response relationship between portal vein fructose levels and net hepatic glucose uptake



Study carried out in 42 h fasted conscious dogs in the presence of hyperglycemia (~200 mg/dl) created by a peripheral glucose infusion and a threefold increase in insulin concentration. Fructose was infused into the portal vein to induce stepwise increases in fructose concentrations. Data are adapted from Shiota *et al.* [15].

In subsequent studies [16] the inclusion of fructose (0.25 mg/kg/min) during a 240 min intraduodenal glucose infusion (8 mg/kg/min) enhanced liver glucose uptake to a greater extent than glucose alone in 42 h fasted dogs. The infusion of glucose alone rapidly increased glucose and insulin levels. This increase was associated with a marked suppression of liver glucose production and the conversion of the liver to a net glucose consumer. The inclusion of fructose in the glucose load markedly blunted both the glucose and insulin response to the duodenal glucose load. Yet liver glucose uptake was increased further because of a marked increase in net hepatic fractional glucose extraction (Fig. 5). The inclusion of fructose did not

Figure 5. Arterial blood glucose level and net hepatic glucose balance in conscious dogs receiving a constant duodenal glucose infusion

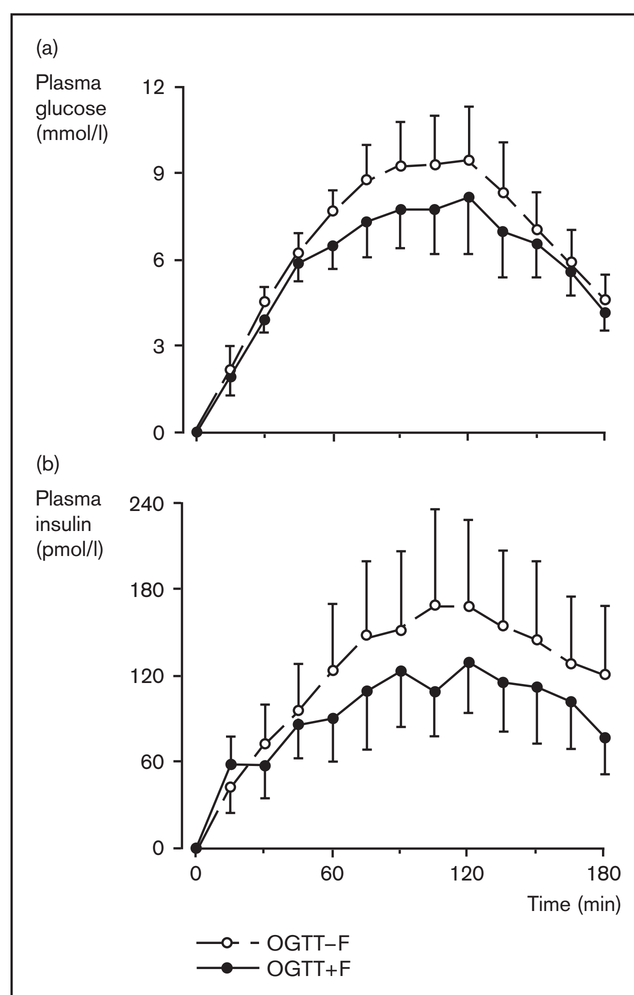


Glucose infusion (8 mg/kg/min) was given in the presence or absence of a fructose infusion (0.4 mg/kg/min). Adapted from Shiota *et al.* [16].

alter the absorption rate of glucose. As was seen with the previous study, liver glycogen synthesis and to a lesser extent lactate release were increased. Thus catalytic quantities of fructose markedly enhance hepatic glucose disposal and glycogen synthesis and improve the glucose and insulin response to a glucose load.

Catalytic quantities of fructose enhance glucose tolerance in both healthy adults and in adults with type 2 diabetes mellitus. Moore *et al.* [17] administered an oral glucose tolerance test (75 g) with or without an additional 7.5 g of fructose to healthy human volunteers ($n = 11$). The inclusion of fructose increased arterial fructose levels by only 0.3 mg/dl. Despite a greater total carbohydrate load with the inclusion of fructose, glucose tolerance was improved by 19%. This improvement could not be explained by an amplification of the insulin response. Interestingly fructose was most effective in the patients who had the poorest glucose tolerance. Fructose is also effective in adults with type 2 diabetes mellitus. Patients with type 2 diabetes mellitus ($n = 5$) were given a 75 g oral glucose load with or without 7.5 g of fructose [18]. The inclusion of fructose blunted both the glucose (↓14%) and insulin (↓21%) response to the oral glucose tolerance test (Fig. 6). The rise in lactate levels was greater in both healthy adults (↑50%) and in adults with type 2 diabetes mellitus (↑100%) when fructose was included in the glucose load. A similar improvement was observed in a rodent insulin resistant model (Zucker fatty *fa/fa* rats [19]). In adults with type 2 diabetes, hyperglycemia induced suppression of endogenous glucose production is defective. The infusion of catalytic doses (0.6 mg/kg min) of fructose restored the glucose-dependent suppression of hepatic glucose production [20].

Figure 6. Change in arterial plasma glucose and insulin levels in adults with type 2 diabetes



Measurements carried out during an oral glucose tolerance test (OGTT; 75 g glucose) (OGTT – F or OGTT + F). Adapted from Moore *et al.* [18].

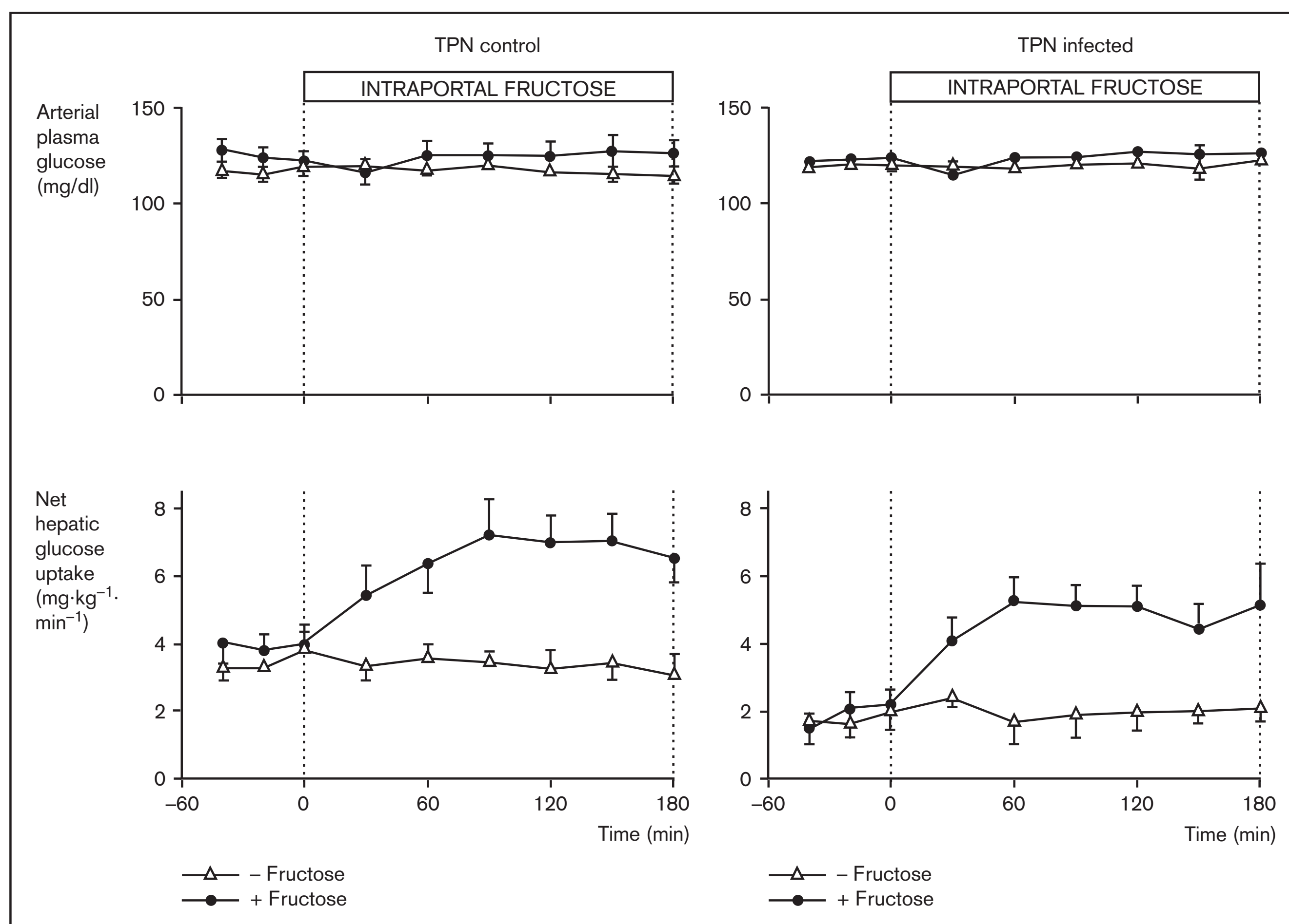
In the dog the augmentation of net hepatic glucose uptake during duodenal glucose infusion by fructose was associated with a rise in glycogen synthesis. Petersen *et al.* [21] examined the effects of a low-dose fructose infusion on liver glycogen synthesis in healthy humans. During a 4 h euglycemic hyperinsulinemic clamp (107 mg/dl; 55 μU/ml) a peripheral infusion of fructose

(0.63 mg/kg/min) was administered. Whole body glucose disposal was unaffected by the fructose infusion. However, on using ^{13}C nuclear magnetic spectroscopy to noninvasively assess the synthesis of liver glycogen, it was increased 2.5-fold. Thus, catalytic doses of fructose augment liver glucose uptake and glycogen synthesis in the acute setting.

Fructose and parenteral nutrition

Fructose has been evaluated as a replacement for glucose in long-term total parenteral nutrition (TPN) to minimize the complications of hyperglycemia. Replacing a substantial quantity of the dietary carbohydrate with fructose led to significant complications. In the case of TPN, infusion of high rates of fructose has the potential to induce lactate acidosis. We recently examined the effect of catalytic quantities of fructose on liver glucose uptake in the TPN adapted state and its interaction with infection (Fig. 7). In a chronically catheterized conscious dog model the liver becomes a major site of glucose removal (4 mg/kg/min) during chronic TPN [22]. However, the liver does not store the glucose carbon; it is released as lactate to be consumed by peripheral tissues. The elevated liver glucose uptake occurs despite only modest hyperglycemia (120 mg/dl) and slightly elevated insulin levels (10 μU/ml). An infusion of somatostatin with replacement doses of insulin and glucagon was given to clamp the insulin and glucagon levels. In this setting of high glycolytic flux and fixed insulin and glucagon levels a constant infusion (0.7 mg/kg/min) of fructose was administered into the portal vein for 3 h. The arterial glucose levels were kept constant by a variable glucose infusion. Fructose infusion increased liver glucose uptake by 2.9 ± 0.4 mg/kg/min. Surprisingly, despite the very high glycolytic flux in the adapted liver, net hepatic lactate release did not increase further. The majority of the glucose carbon was deposited as glycogen.

Figure 7. Arterial plasma glucose concentration and net hepatic glucose uptake in normal (TPN control) and infected (TPN infected) dogs adapted to total parenteral nutrition (TPN)



Fructose (0.7 mg/kg/min) or saline was infused intraportally for 180 min. Adapted from Donmoyer *et al.* [22].

Fructose is also able to overcome stress induced impairments in liver glucose uptake. Infection impairs the hepatic adaptation to TPN despite marked hyperinsulinemia [23]. The decrease in liver glucose uptake is accompanied by a marked decrease in hepatic glycolysis as well. To determine if fructose could correct the infection induced impairment in liver glucose uptake, infected animals adapted to TPN received an infusion of somatostatin with replacement doses of insulin and glucagon to match the elevated levels seen during infection. Fructose (0.7 mg/kg/min) was then infused into the portal vein of infected dogs for 3 h. The arterial glucose levels were maintained constant by a variable glucose infusion. Interestingly, the effectiveness of fructose in augmenting liver glucose uptake was not altered by the presence of infection. Fructose infusion increased liver glucose uptake by 2.5 ± 0.3 mg/kg/min. As was seen in the noninfected setting, the majority of the glucose carbon was diverted to glycogen. Moreover, in the TPN-adapted setting, despite the high rate of glycolysis, glycogen synthesis is the main metabolic fate of the fructose induced increase in liver glucose uptake.

While fructose is beneficial in an acute setting where glycogen synthesis is the main metabolic fate of the glucose, in the chronic setting where glycolysis and subsequent lactate release is the main metabolic fate of the glucose, the benefits on liver glucose disposal do not persist. In a recent study we asked if the chronic inclusion of fructose during TPN would attenuate the infection induced decrease in liver glucose uptake. In this study dogs were allowed to adapt to the TPN then an infection was induced [24]. At the onset of infection in one group of animals fructose was added to the TPN (1 mg/kg/min), while in the second group fructose was not added to the TPN. After 2 days liver glucose metabolism was assessed. Infection suppressed liver glucose uptake and the inclusion of fructose in the TPN did not attenuate the hyperglycemia or hyperinsulinemia nor did it improve liver glucose uptake. Interestingly, when the chronic fructose infusion was acutely discontinued liver glucose uptake was markedly suppressed. The rapid decrease in liver glucose uptake was due to a suppression of both glucose entry and an activation of glycogenolysis. Thus a sustained chronic exposure to fructose will lead to a persistent enhancement in glucokinase translocation. This increase alone, however, will not lead to a persistent enhancement in liver glucose uptake because other adaptations within the liver limit the effectiveness of this increase.

These results are consistent with clinical trials in individuals with diabetes. A combination of fructose, xylitol and glucose (ratio 1:1:2) was compared with glucose alone in parenteral nutrition [25]. Interestingly, in nonseptic patients with diabetes insulin requirements were lower when glucose was replaced with the combination of glucose, fructose and xylitol. In septic patients, however, insulin requirements were higher when the mixture was infused. It is unclear if the lack of beneficial effects of fructose in the septic population is related to the relatively high doses of fructose used in these studies compared with the catalytic doses used in previous studies. Since fructose was given parenterally at higher than catalytic doses a greater fraction of the fructose may be removed by peripheral tissues, which could impair glucose tolerance. An additional possibility is that the chronic inclusion of fructose in TPN has limited benefit, as was observed in the infected animal model. This is presumably because during TPN glycogen synthesis is not the final metabolic fate of glucose, it is glycolysis. Activation of glucokinase minimally activates glycolysis, thus it would be of limited long-term benefit in TPN in improving liver glucose uptake in insulin resistant states unless it were the sole defect in hepatic glucose metabolism, which is clearly not the case.

Conclusion

The impact of fructose on glucose homeostasis is determined by the quantities of dietary fructose included in the diet. When large nutritive quantities of fructose are used glucose intolerance and hypertriglyceridemia occur. Inclusion of small catalytic quantities of fructose in a carbohydrate meal improves glucose tolerance. This improvement is primarily mediated by the activation of hepatic glucokinase and consequent facilitation of liver glucose uptake. The improvement in glucose tolerance is most evident in insulin resistant settings (e.g. type 2 diabetes and infection). The beneficial effect of catalytic quantities of fructose on hepatic glucose disposal, however, does not persist if fructose is given continuously such as in TPN. The ineffectiveness of fructose in this setting may be due to the limited role glucokinase plays in the hepatic adaptation to continuous nutritional support rather than to the inability of fructose to chronically facilitate the activation of glucokinase. Facilitation of hepatic glucose entry is most effective in insulin resistant patients in the acute setting when liver glycogen synthesis is the primary metabolic fate of glucose. Thus, activating glucokinase during a carbohydrate meal may serve to minimize the hyperglycemia seen in insulin resistant settings where underlying defects in hepatic glucose disposal are present.

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