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Hepatic adaptations to sucrose and fructose☆

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Abstract

The liver is an important site of postprandial glucose disposal, accounting for the removal of up to 30% of an oral glucose load. The liver is also centrally involved in dietary lipid and amino acid uptake, and the presence of either or both of these nutrients can influence hepatic glucose uptake. The composition of ingested carbohydrate also influences hepatic glucose metabolism. For example, fructose can increase hepatic glucose uptake. In addition, fructose extraction by the liver is exceedingly high, approaching 50% to 70% of fructose delivery. The selective hepatic metabolism of fructose, and the ability of fructose to increase hepatic glucose uptake can, under appropriate conditions (eg, diets enriched in sucrose or fructose, high fructose concentrations), provoke major adaptations in hepatic metabolism. Potential adaptations that can arise in response to these conditions and putative mechanisms driving these adaptations are the subject of this review.

1. Introduction

The central role of the liver in glucose homeostasis has been recognized since the time of Claude Bernard. The liver can both provide glucose to and remove glucose from the circulation [1-4]. The quantitative contribution of glucose production and uptake to glucose homeostasis is, in large part, determined by the metabolic state of the organism. The transition between the fasted and fed states is characterized by profound changes in circulating nutrients, hormones, and neural signals. Changes in this combination of signals ultimately determine the direction (net production vs net uptake) of liver glucose metabolism [5,6].

The liver is a major contributor to the disposition of enterally delivered glucose, taking up 20% to 30% of absorbed glucose [6]. Phosphorylation of glucose by glucokinase is a rate-determining step in hepatic glucose metabolism. Low "catalytic" doses of fructose increase glucose uptake by increasing the cytosolic availability of glucokinase [7]. Fructose is now an abundant source of dietary carbohydrate in the United States [8,9]. In contrast to glucose, phosphorylation of fructose in the liver occurs via the enzyme fructokinase. In addition, the metabolism of fructose 1-phosphate in the liver occurs independently of phosphofructokinase, a second rate-determining step in glucose metabolism [10,11]. As a result, the liver is the primary site of fructose extraction and metabolism, with extraction approaching 50% to 70% of fructose delivery [11]. Therefore, increased availability of fructose (eg, high-fructose corn syrup) will increase not only "normal" glucose flux but also fructose metabolism in the hepatocyte.

2. Liver sensitivity to nutrients

The responsiveness of the liver to changes in the composition and rate of nutrient delivery is predicted based on its anatomic position and regulatory features that appear to be specific to this organ. The portal vein is the primary blood supply to the liver. This vessel not only receives the bulk of absorbed amino acids and carbohydrates, but is also the site for pancreatic hormone and gastrointestinal peptide release. Thus, the anatomic position of the liver places it in a strategic buffering position for absorbed carbohydrates and amino acids.

In the postabsorptive state, glucose release by the liver is achieved by the dephosphorylation of glucose 6-phosphate derived from both glycogenolysis and gluconeogenesis by the enzyme glucose 6-phosphatase. Gluconeogenic flux requires oxidative substrate and carbon precursors; thus, the regulation and magnitude of gluconeogenesis, and therefore glucose release, are intimately linked to free fatty acid and gluconeogenic precursor delivery [12-17].

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In the postprandial state, the liver becomes a glucose-consuming organ. The liver is also critically involved in dietary lipid and amino acid uptakes, and the presence of either or both of these nutrients can reduce hepatic glucose uptake [5,18]. The composition of ingested carbohydrate also influences hepatic glucose metabolism [11,19]. For example, fructose (0.02-0.2 mmol/L) increases hepatic glucose uptake and glycogen synthesis [20-22]. In rats, the ingestion of a single meal containing 68% of energy from corn starch reduced glucose 6-phosphatase catalytic subunit gene expression and enzyme activity, whereas a meal containing 68% of energy from sucrose (a high-sucrose diet) increased catalytic subunit gene expression and enzyme activity when compared with fasted controls and rats refed with corn starch [23]. In addition, whereas hyperglycemia and hyperinsulinemia, brought about by using the glucose clamp technique, resulted in decreased glucose 6-phosphatase catalytic subunit gene expression compared with fasted controls, addition of a fructose infusion, which elevated portal vein fructose concentrations to ~1 mmol/L (a concentration of fructose achieved in response to a meal enriched in sucrose, 68% of energy as sucrose) [23], increased catalytic subunit gene expression and enzyme activity [24]. Thus, the composition of nutrients presented to the liver can have a profound effect on hepatic glucose metabolism.

Fructose extraction and metabolism by the liver are exceptionally high (relative to glucose) due both to the extensive amount of fructokinase in the liver (the enzyme that phosphorylates fructose to fructose 1-phosphate) and to the subsequent metabolism of fructose 1-phosphate at the triose phosphate level, which bypasses flux control at phosphofructokinase [2,11,20,24-26]. Previous studies comparing the metabolism of fructose and glucose in post-absorptive humans over short intervals have shown that fructose is used faster than glucose and that more is converted to liver glycogen [27,28]. The concentration of fructose required to provoke hepatic adaptations is currently uncertain. In human volunteers, a constant infusion of fructose that achieved steady-state, supraphysiologic levels of 6 to 8 mmol/L reduced liver adenosine triphosphate (ATP) and inorganic phosphate (Pi) concentrations to ~71% and 55% of control values after 25 minutes [29]. Similar data were obtained in the perfused rat liver [29] and by others in both humans and the rat [30,31]. Intravenously infused fructose (achieving steady-state fructose concentrations of ~2 mmol/L) had effects on splanchnic amino acid and carbohydrate metabolism that were distinct from that of glucose (~9 mmol/L) in hypertriglyceridemic men [32]. In rats, intraperitoneal doses of fructose (40 nmol/kg) resulted in rapid increases in glycolytic metabolites and reductions in total adenylate compounds in the liver [33].

What are the concentrations of fructose likely to be attained in the portal vein? In a review by Mayes [11], it was reported that in humans and baboons, maximal fructose concentrations of 2.2 mmol/L were observed after a high-fructose or high-sucrose meal [11,34,35]. In humans, a maximum fructose concentration of 1 mmol/L was recorded in peripheral blood [35]. In rats, a large fructose meal provided by gastric intubation produced portal vein concentrations of 1.1 to 2.2 mmol/L [11,36]. We have more recently demonstrated that a single high-sucrose meal (68% of energy from sucrose) provided to rats ad libitum for 3 hours produced portal vein fructose concentrations of 1.4 ± 0.2 mmol/L [23]. Provision of a single sucrose meal containing 18% of energy as sucrose to rats elicited portal vein fructose concentrations of 0.6 ± 0.1 mmol/L after a 3-hour refeeding period [37]. Thus, it is likely that physiological, postprandial concentrations of fructose in the portal vein range from 0 to peak concentrations of 0.5 to 1.0 mmol/L.

More recent studies have been performed to ascertain the immediate effects of fructose on glucose metabolism in humans [38-41]. Ingestion of either 0.5 or 1 g/kg of fructose or infusion of fructose (22 μmol · kg^{-1} · min^{-1}) had little effect on overall glucose appearance despite increased glucose production from fructose [38,39]. Fructose oxidation represented a significant portion of fructose metabolism accounting for 56% to 59% of the ingested fructose and ~33% of the infused fructose. It is likely that extrahepatic lactate oxidation subsequent to hepatic fructolysis contributed significantly to the estimated rate of fructose oxidation. Thus, increments in fructose that elicited peak arterial concentrations of 0.3 to 0.4 mmol/L after ingestion and ~1 mmol/L after infusion produced immediate changes in hepatic and extrahepatic substrate metabolism, but did not induce quantitative changes in overall glucose production. Nuttall et al also demonstrated that the ingestion of 50 g of fructose with 500 mL of water did not elicit a significant change in circulating glucose concentrations when compared with water alone in normal healthy men [42]. An immediate (3 hours) fructose infusion (16.7 μmol · kg^{-1} · min^{-1}, a rate approximately 25% less than reported previously) in humans induced both hepatic and extrahepatic insulin resistance. These data are consistent with the notion that high concentrations of fructose elicit adaptations in the liver that include metabolic intermediates, gene expression, and insulin action. The extent to which these hepatic adaptations occur in the context of usual dietary sucrose and fructose intake in humans is presently unclear.

3. Fructose absorption

Fructose, glucose, and galactose are the 3 major dietary monosaccharides. Sucrose (glucose-fructose), lactose (glucose-galactose), and maltose (glucose-glucose) are the major disaccharides. Dietary fructose, therefore, occurs in 2 forms: mono- or disaccharide [43]. Glucose and galactose share a transporter and are efficiently absorbed and actively transported across the intestinal epithelium [43]. Mannose crosses the epithelium slowly, via passive diffusion [43,44]. The rate of fructose absorption appears to be between that of mannose and glucose [35]. Fructose is absorbed by carrier-mediated facilitated diffusion, an energy-dependent process. The

fructose carrier is a member of the glucose transport family and is referred to as GLUT5 [43]. Sucrose is cleaved to glucose and fructose by sucrase, an enzyme located in the brush border of small intestine enterocytes [45]. A high-sucrose diet (60% of energy as sucrose) increased sucrase activity after 2 days in human subjects [45]. For reasons not understood, the absorptive capacity for fructose derived from sucrose exceeds that of fructose monosaccharide in healthy individuals [46]. Therefore, fructose, as an isolated nutrient, is incompletely absorbed even in healthy subjects [43,44,47]. In one study, up to 80% of healthy subjects experienced incomplete absorption of 50 g of fructose [43]. Fructose has increasingly been used as a sweetener since the introduction of high-fructose corn syrups in the 1960s [9,43,48]. Importantly, fructose absorption after ingestion of fructose alone has not been compared with absorption of fructose contained in high-fructose corn syrup. Future studies, designed to examine the absorption of high-fructose corn syrup, will be important to our understanding of hepatic and systemic delivery of dietary fructose.

4. Unique regulation of hepatic glucose uptake by fructose

Multiple, now classic, studies demonstrated that efficient hepatic glycogen synthesis required the presence of glucose plus gluconeogenic precursors, such as glycerol, lactate, or fructose [2,4,49-51]. More recently, fructose-mediated stimulation of glucose phosphorylation in rat hepatocytes, glucose uptake in the dog, and glycogen synthesis in rats, dogs, and humans have been observed [20-22,27,52-56]. Phosphorylation of glucose is a rate-determining step for hepatic glucose metabolism. In the postabsorptive or fasted state, glucokinase in the liver is localized in the nucleus, where it is bound to the glucokinase regulatory protein [7,57,58]. Fructose 6-phosphate binding to the glucokinase regulatory protein favors interaction with and sequestration of glucokinase in the nucleus. Fructose 1-phosphate, the phosphorylated product of fructose in the liver, competes with fructose 6-phosphate for binding to the glucose regulatory protein [59]. In this way, fructose 1-phosphate can elicit the translocation of glucokinase from the nucleus to the cytosol, where this protein can gain access to free glucose [60]. As a result, fructose can reduce the glycemic response to an oral glucose load in normal adults and intraduodenal glucose infusion in conscious dogs [20,61]. However, previous work demonstrated little effect of fructose in lowering the plasma glucose response in type 2 diabetic patients when ingested as a mixture of glucose and fructose or sucrose despite stimulation of insulin secretion [62]. It is likely that the effect of low doses of fructose to stimulate glucose uptake and glycogen synthesis, and influence the plasma glucose response, will be modified when ingested in the context of a mixed meal [63]. Thus, the proposed catalytic effect of fructose on glucose uptake and glycogen synthesis may only play a minor role in overall postprandial hepatic carbohydrate metabolism.

5. Quantitative impact on the liver

After ingestion of an oral glucose load the liver becomes a net glucose-consuming organ, accounting for removal of 20% to 30% of the absorbed glucose [5,6,64]. Most of this glucose is used to replenish glycogen stores with the remainder primarily directed to glycolysis [6,65]. The high rate of fructose extraction by the liver coupled with the ability of fructose 1-phosphate to stimulate glucose uptake predicts that elevation of the fructose concentration will increase the contribution of the liver to the disposal of dietary carbohydrate (glucose + fructose). This “extra” carbohydrate should lead to increased liver glycogen concentrations [4,21,53] but may also increase flux through one of several additional hepatic pathways, including glycolysis, the pentose phosphate pathway, and/or de novo lipogenesis [11,66,67]. When normal men ingested a 50-g fructose load with 500 mL of water there was a large, transient increase in lactate and alanine concentrations [42]. It is likely that the relative contributions of these pathways will be both time and dose dependent [55,56,65]. In addition, the relative carbon flux through glycolysis and glycogenesis will be significantly affected by the concentration of fructose 2,6-bisphosphate [68].

6. An animal model to study hepatic adaptations to increased fructose delivery

We and others have used high-sucrose diets to investigate the immediate response of the liver to postprandial fructose exposure [23,69]. To test the hypothesis that the presence of high fructose concentrations can induce a unique intrahepatic environment, male rats were fasted and then either remained fasted or were refed with diets containing either 68% of energy from corn starch, 12% corn oil, and 20% casein (STD), or 68% sucrose, 12% corn oil, and 20% casein (HSD) for 3 hours. Despite similar energy intake, liver concentrations of xylulose 5-phosphate, lactate, and diacylglycerol were significantly increased and Pi significantly decreased in HSD vs STD (Table 1) [23]. Importantly, a diet containing 18% of energy as sucrose, 50% corn starch, 12% corn oil, and 20% casein elicited lower Pi (1.8 ± 0.2 μmol/g) and higher xylulose 5-phosphate (36.2 ± 3.9 nmol/g) after 3 hours of refeeding when compared to STD [37]. When the portal vein fructose concentration was selectively elevated to ~1 mmol/L under hyperglycemic and hyperinsulinemic conditions, hepatic concentrations of xylulose 5-phosphate were 49.2 ± 4.2 nmol/g, whereas they were 10.2 ± 1.2 in the absence of fructose and 15.3 ± 1.8 when fructose in the portal vein was selectively increased to 0.3 ± 0.1 mmol/L [24]. The immediate hepatic response to ingestion of a high-sucrose diet or a 3-hour elevation in the fructose concentration included increased glucose 6-phosphatase gene expression and reduced serine phosphorylation of glycogen synthase kinase-3 and CREB [23,24]. In addition, when the selective elevation of portal vein fructose concentrations to

Table 1
Hepatic concentrations of lactate, xylulose 5-phosphate, diacylglycerol, and Pi in fasted rats or in fasted rats that were refed starch-enriched or sucrose-enriched (HSD) diets for 3 hours [23]

	Fasted	Refed STD	Refed HSD
Lactate (μmol/g)	0.3 ± 0.05	0.6 ± 0.1	1.2 ± 0.2*
Xylulose 5-phosphate (nmol/g)	1.7 ± 0.4	18.5 ± 3.1**	63.4 ± 5.4*
Diacylglycerol (μmol/g)	0.15 ± 0.03	0.3 ± 0.06	0.7 ± 0.1*
Inorganic phosphate (μmol/g)	2.6 ± 0.4	2.9 ± 0.6	1.1 ± 0.5*

Value are means ± SEM (n = 6-8). Fasted indicates 48-hour fast; refed STD, 48-hour fasted rats that were refed a diet containing 68% of energy from corn starch, 12% from corn oil, 20% from casein; refed HSD, 48-hour fasted rats that were refed a diet containing 68% of energy from sucrose, 12% from corn oil, 20% from casein.

* $P < .05$, significantly different from other 2 groups.

** $P < .05$, significantly different from fasted group.

Table 2
Body composition and lipid profile of rats fed with either a high-starch diet (STD) or high-sucrose diet (HSD) for 1 to 30 weeks

	HSD vs STD	Duration (wk)
Body weight gain		
Body fat	ND	1-30
Free fatty acids	ND	1-30
Triglycerides		
Blood	Increased	1-30
Liver	Increased	1-30
Muscle	ND	1-30
Fatty acid composition		
Liver (sinusoid)	Increased saturated fatty acids	1-30
Muscle	ND	1-30

Data obtained from 6 to 8 fasted rats after 1, 2, 5, 8, 16, or 30 weeks on diet. Data are summarized based on previously published results [71,72,74]. ND indicates not significantly different.

~1 mmol/L was prolonged from 3 to 6 hours, the liver was characterized by increased hepatic c-Jun terminal kinase activity and phosphorylation of insulin receptor substrate 1 on serine 307 [70]. The extent to which these responses are mediated by xylulose 5-phosphate, Pi and/or diacylglycerol is currently under investigation.

6.1. Phenotypic changes in male rats after long-term exposure to diets enriched in sucrose or fructose

We have examined the impact of long-term exposure to high-sucrose diets in rats to determine the potential consequences of this unique nutrient. Male rats were pair-fed with diets enriched with either corn starch (STD) or sucrose (HSD) for periods ranging from 1 to 30 weeks [71,72]. The HSD increased blood (Fig. 1) and liver triglyceride content and the saturated fatty acid composition of hepatic triglycerides and sinusoidal membrane phospholipids [71-73]. These differences were observed after only 1 week on the HSD, were maintained for up to 30 weeks, and were not accompanied by differences in body weight or composition (Table 2, Fig. 1). They were also observed in 2 different strains of rats, Wistar and Sprague-Dawley [71,74-76]. Similar adaptations occur in response to a fructose-enriched diet containing 34% of energy from fructose and 34% from glucose [77] and in response to diet containing 18% of energy as sucrose [71]. Some or all of these adaptations have been observed by others [25,78-89].

Basal (6-8 hours fasted) levels of glucose, free fatty acids (Fig. 1), glucagon, and corticosterone were not significantly different between STD and HSD [71,72,74,75]. Basal insulin levels were not significantly increased in HSD after 1 or 2 weeks, but fasting hyperinsulinemia was observed in

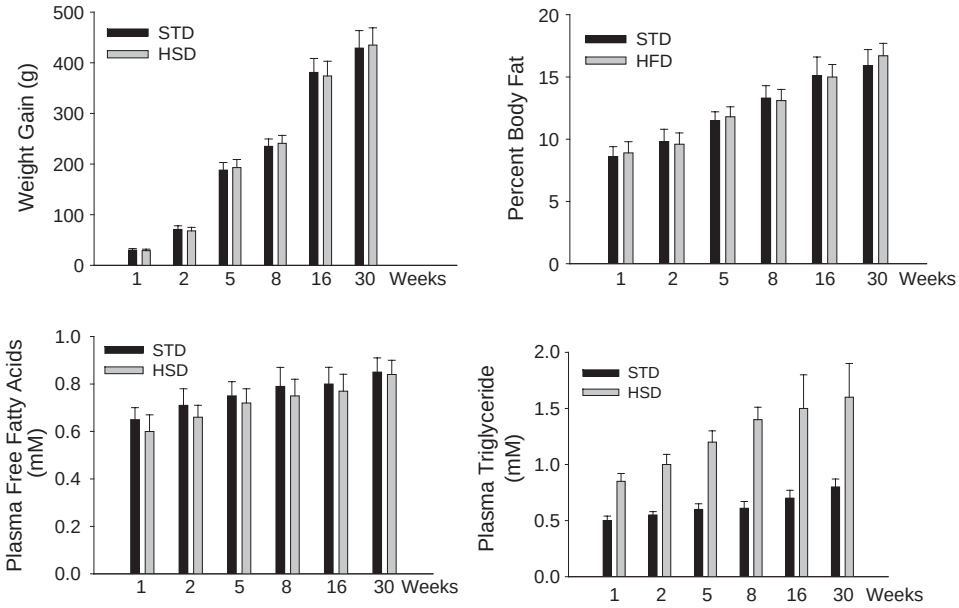

Fig. 1. Body weight gain (top, left), percentage of body fat (top, right), plasma free fatty acids (bottom, left), and plasma triglycerides (bottom, right) in 6- to 8-hour fasted male rats. Data are means ± SEM (n = 6-10 per group) [71,72,74]. Plasma triglycerides were significantly ($P < .05$) increased in HSD vs STD at all time points. Percentage of body fat was determined chemically.

Table 3
Whole body and tissue-specific glucose metabolism in STD and HSD

	HSD vs STD	Time frame (wk)
Basal glucose metabolism		
Glucose production (Ra)	ND	1-30
Glucose use (Rd)	ND	1-30
Skeletal muscle R'g	ND	1-30
Adipose tissue R'g	ND	1-30
Insulin suppression of Ra	Reduced	1-30
Insulin stimulation of Rd	Reduced	2-30
Insulin stimulation of skeletal muscle R'g*	Reduced	2-30
Insulin stimulation of adipose tissue R'g*	Reduced	2-30

Data obtained from 6 to 8 fasted rats after 1, 2, 5, 8, 16, or 30 weeks on diet, except where noted by asterisk [71,72,90,91]. R'g indicates tracer-estimated glucose uptake; Ra, tracer-determined rate of glucose appearance; Rd, tracer-determined rate of glucose disappearance.

HSD at 5 weeks (ie, induction of fasting hyperinsulinemia occurs between 2 and 5 weeks). These data suggest that the HSD produced whole body insulin resistance between 2 and 5 weeks (based on fasting insulin levels). To more closely examine insulin action in this model and the relationship between HSD-induced changes in lipid profile and insulin action, euglycemic, hyperinsulinemic clamps were performed in combination with 3-^{3}H-glucose (to estimated glucose production and use) and/or 2-deoxy-[1-^{14}C]glucose (to estimated individual tissue glucose uptake) [71,72,90,91]. Basal (6-8 hours fasted) glucose kinetics and basal tissue-specific glucose uptake were not significantly different between the 2 dietary groups (Table 3). Insulin suppression of glucose production was significantly reduced after 1 week in HSD, whereas insulin stimulation of glucose use was significantly reduced between 2 and 5 weeks. Likewise, insulin stimulation of skeletal muscle and adipose tissue glucose uptake was significantly reduced between 2 and 5 weeks [90,91] (or unpublished observations). These data demonstrate that HSD-induced insulin resistance occurs initially in glucose-producing tissues (liver, kidney) and is later followed by impairments in skeletal muscle and adipose tissue. Importantly, a lower sucrose diet (18% of energy as sucrose) also leads to insulin resistance in rats, which is primarily localized to the liver [71]. Multiple groups have also documented increased blood and tissue lipids, insulin resistance, and in some cases hypertension after long-term exposure to diets enriched in sucrose [79,82,83,88,92-97] or fructose [88,98-106] in rats. However, there are a small proportion of animal studies that have not observed some or all of these adaptations [107-109].

6.2. The early appearance of sucrose-induced impairments in insulin suppression of glucose production involves direct effects on the liver

Tracer-estimated glucose appearance represents the sum of glucose release from the liver and kidney. To establish that the liver contributed to sucrose-induced impairments in insulin regulation of glucose appearance, liver perfusions were performed. Insulin suppression of liver glucose output was significantly reduced in HSD compared to STD at both 1 (unpublished observations) and 5 weeks [110]. Thus, sucrose-induced impairments include direct effects on hepatic insulin action and involve multiple postreceptor insulin signaling steps, including tyrosine phosphorylation of insulin receptor substrate proteins (IRS) 1 and 2, interaction of phosphoinositide (PI) 3-kinase with IRS proteins, and phosphorylation of Akt [111]. A high-fructose diet also results in impairments in hepatic insulin signaling [104].

6.3. Antagonists of insulin action in the liver

Insulin has both direct and indirect effects on glucose production. Indirect effects include the ability of insulin to suppress adipose tissue lipolysis and free fatty acid concentrations, insulin modulation of adipokines, insulin suppression of glucagon secretion, and insulin signaling in the hypothalamus [112-117]. Each of these indirect effects can influence either the total glucose production or the relative contributions of glycogenolysis and gluconeogenesis to total glucose production. Importantly however, our studies in perfused liver demonstrate clearly that sucrose-induced insulin resistance must involve intrahepatic impairments [110]. In addition, sucrose- and fructose-induced insulin resistance can be elicited in the absence of body fat accumulation, elevations in circulating free fatty acids, and elevations in glucagon [72,88,95]. Whether hypothalamic insulin signaling is impaired in this model is presently unknown.

Insulin signaling can be attenuated by the actions of tyrosine phosphatase and serine kinase proteins. Two examples of such proteins are protein tyrosine phosphatase 1B (PTP1B) and c-Jun N-terminal kinase (JNK). Protein tyrosine phosphatase 1B negatively regulates insulin receptor and IRS phosphorylation and has recently been implicated in the regulation of insulin signaling in liver and adipose tissue [118,119]. c-Jun N-terminal kinase, or stress-activated protein kinase, which can be activated by a number of stimuli including cytokines, some fatty acids, and redox state, can also interfere with proximal steps in the insulin signaling pathway [120,121]. A recent study demonstrated not only that JNK activity was increased in animal models of obesity, but also that the absence of this protein reduced adiposity and improved insulin action in 2 different mouse obesity models [121]. Recent studies have observed increased expression of PTP1B protein in livers from fructose-fed hamsters [122] and increased phosphorylation of JNK and elevated activator protein-1 activity (a downstream target of JNK) in livers taken from rats fed a high-fructose diet for 2 weeks [123]. To determine the potential contribution of these 2 proteins to the early impairments in hepatic insulin action in response to dietary sucrose, we have evaluated the time course of changes in PTP1B and JNK activity in liver. A high-sucrose diet resulted in increased hepatic PTP1B activity and protein levels after ~3 weeks, whereas JNK activity was increased

after 1 week (note that hepatic insulin resistance was present after only 1 week) [124]. Furthermore, the selective elevation of portal vein fructose concentrations to ~1 mmol/L under hyperinsulinemic, hyperglycemic conditions resulted in increased hepatic JNK activity (without affecting PTP1B) that required 3 to 6 hours [70]. Thus, these data suggest that changes in PTP1B are not critical to the early development of hepatic insulin resistance in this model. In contrast, the time course of sucrose-induced hepatic insulin resistant coincided with the presence of increased hepatic JNK activity. Normalization of the elevated JNK activity in hepatocytes isolated from sucrose-fed rats improved but did not completely restore insulin action, based on measurements of tyrosine phosphorylation of IRS proteins and glucose release [70].

7. Mediators of JNK activation: hepatic stress in response to fructose metabolism

The activation of JNK by high-fructose and high-sucrose diets or fructose infusion in rats suggests that the hepatic response to elevated fructose concentrations includes inflammatory pathways [70,123]. Kelley et al [123] reversed high-fructose diet–induced hypertriglyceridemia and reduced activator protein-1 activation with lipoxygenase inhibitors. They suggested that hepatic metabolism of fructose, under conditions of high fructose delivery, may generate stress-activating molecules such as methylglyoxal (a highly reactive ketoaldehyde) and/or D-glyceraldehyde which can serve as substrates for glyceraldehyde-derived advanced glycation end products [123]. Aldehydes, such as methylglyoxal, are extremely reactive as glycating agents for enzymes and other cellular components [125]. Consistent with this notion, rats consuming a fructose-enriched diet (10% of energy) were characterized by elevated levels of aldehydes, particularly methylglyoxal [126]. Activation of hepatic JNK in response to a single, high-sucrose meal or fructose infusion required a significant period (3-6 hours), suggesting that the intrahepatic signal(s) involved may not be typical carbohydrate intermediates (eg, phosphorylated sugars, xylulose 5-phosphate, lactate) [70]. Accumulation of precursors that generate advanced glycation end products may be consistent with this delayed time course of JNK activation. In tissue culture experiments, high fructose concentrations were significantly more reactive (ie, DNA damage, interaction with hemoglobin) than high glucose concentrations [127-129]. Treatment of fructose-fed rats with vitamin B_6, C, or E lowered elevated cytosolic calcium and reduced tissue aldehyde conjugates [126]. Metformin, which has been used to lower elevated plasma methylglyoxal concentrations in type 2 diabetic subjects [130], was also able to prevent the development sucrose-induced insulin resistance and cardiomyocyte dysfunction in rats [131]. Additional studies will be required to determine whether there is a causal relationship between aldehydes and JNK activation in the liver. In addition, studies are underway to identify the upstream kinases that link fructose metabolism to JNK activation in the hepatocyte.

8. Cellular intermediates

There are a number of potential regulatory consequences to the unique intrahepatic environment that is created by ingestion or infusion of large amounts of fructose that should be briefly discussed. Hepatic disposal of large amounts of fructose can increase fructose 1-phosphate, xylulose 5-phosphate, fructose 2,6-bisphosphate, Pi, adenosine monophosphate (AMP), and adenosine diphosphate, and reduce cellular ATP [11,23,24,30,33,55,56,69,132]. This small and incomplete list of changes that are either unique to or of greater magnitude when large amounts of fructose are presented to the liver underscores the complex environment and multitude of signals that confronts the hepatocyte.

Fructose 1-phosphate can increase translocation of glucokinase to the cytosol and glucose phosphorylation and inhibit glycogen phosphorylase [54,55,60]. Thus, this intermediate may play an instrumental role in the regulation of glycogen accumulation when fructose delivery is increased. Xylulose 5-phosphate appears to regulate glucose-induced lipogenesis via activation of a xylulose 5-phosphate–activated protein phosphatase in the liver [133]. Thus, the magnitude of lipogenesis in response to fructose delivery may be, in part, tied to carbon entry into the pentose phosphate pathway. Fructose 2,6-bisphosphate, a potent regulator of the activities of phosphofructokinase and fructose 1,6-bisphosphatase [68], accumulates in response to a high-sucrose meal [69]. Such a change in fructose 2,6-bisphosphate would be expected to activate the former and inhibit the latter enzyme, and thus favor glycolytic flux. However, even in the presence of elevated fructose 2,6-bisphosphate concentrations, there remains active flux through gluconeogenesis, and thus indirect pathway glycogen synthesis [4]. Recent studies have demonstrated that fructose 2,6-bisphosphate can stimulate glucokinase gene expression in an insulin-independent manner and can secondarily affect glucose 6-phosphatase gene expression by lowering the plasma glucose concentration in diabetic mice [134]. Thus, cellular regulation of glucose flux by this intermediate appears to be quite complex and likely dependent on factors such as concentration and the interaction among intermediates within the hepatocyte. Indeed, Nishimura and Uyeda [135] demonstrated that xylulose 5-phosphate–activated protein phosphatase catalyzes the dephosphorylation of fructose 6-phosphate, 3-kinase: fructose 2,6-bisphosphatase, and thus can contribute to the concentration/accumulation of fructose 2,6-bisphosphate in the liver.

Large amounts of ingested sucrose or infused fructose activate JNK activity in the liver and hepatocyte [70]. Large doses of fructose also increase AMP and reduce ATP concentrations [11,30,136]. Sustained activation of AMP-activated protein kinase can induce JNK activation in liver cells [137]. Adenosine monophosphate–activated protein kinase may also play a role in glucose-mediated regulation of gene expression and the reciprocal regulation of triacylglycerol synthesis and fatty acid oxidation in the liver [138,139].

Thus, in future studies it will be important to examine the precise role of AMP-activated kinase in the liver, especially with regard to the relationship between nutrient delivery and the regulation of triglyceride synthesis and lipid oxidation. Certainly, fructose-mediated changes in the concentration of adenine nucleotides would be expected to modulate oxidative phosphorylation and the relative flux between glycolysis and gluconeogenesis in the liver [140]. The important question to be considered and experimentally tested is how signals elicited by changes in adenine nucleotides interact with and are modified by concomitant changes in other cellular intermediates, such as fructose 1-phosphate and xylulose 5-phosphate.

9. Role of hepatic lipids

Fatty liver is a characteristic feature of type 2 diabetes, with estimates of prevalence ranging from 21% to 78% [141,142]. A recent study demonstrated that type 2 diabetic subjects with fatty liver were significantly more insulin resistant when compared with type 2 diabetic subjects without fatty liver [143]. Dietary and circulating lipids also influence insulin action and glucose metabolism in the liver [6,144-146]. In rats, long-term exposure to sucrose- or fructose-enriched diets leads to fatty liver, and treatments that reduce or prevent hepatic lipid accumulation improve insulin action and glucose metabolism in the liver [72,88,90,95]. Thus, it is important to consider the role of hepatic lipids in the metabolic perturbations induced by high-sucrose and high-fructose diets.

We have demonstrated that a high-sucrose diet increased in vivo gluconeogenesis in male rats (assessed using ^3H_2O) and the capacity for gluconeogenesis in both perfused livers and isolated hepatocytes [76,110,147]. This adaptation was observed after only 1 week of diet exposure. When hepatocytes were exposed to bromopalmitate, an inhibitor of fat oxidation, in the absence of exogenous fatty acids, the sucrose-induced increase in gluconeogenesis was abolished [147]. A causal relationship was recently reported between high-fat diet–induced hepatic steatosis and accelerated gluconeogenesis in rats [148]. These data suggest that accelerated endogenous lipid oxidation may mediate the sucrose-induced increase gluconeogenesis.

Infusion of lipid emulsions that immediately elevate free fatty acid levels leads to hepatic insulin resistance and is associated with a progressive and selective increase in hepatic protein kinase C (PKC)–δ translocation in rats (or activation) [149]. Evidence supporting a causal relationship between hepatic fat accumulation and hepatic insulin resistance, mediated in part via activation of PKC-ε, was recently demonstrated in rats [148]. One can therefore postulate that the elevation of hepatic lipids after exposure to high-sucrose or high-fructose diets may contribute to hepatic insulin resistance through activation of PKC isoforms. However, we did not observe differences in the abundance of several PKC isoforms including PKC-δ in liver cytosolic and membrane fractions isolated from rats after long-term or short-term exposure to either high-sucrose or high-starch diets, or immediate fructose infusions [70]. Thus, the extent to which fatty liver contributes to sucrose- and fructose-induced hepatic insulin resistance is uncertain.

10. Oxidative stress

Oxidative stress, defined as a shift in the prooxidant-antioxidant balance toward oxidants, has been proposed as a causative factor in the pathogenesis of many diseases [150,151]. In general, the contribution of oxidative stress to hepatic adaptations in response to high-sucrose or high-fructose diets appears to be minor. Although a high-sucrose diet reduced liver glutathione *S*-transferase activity and cytochrome *P*450 [152], increased lipid peroxidation was only observed in the heart and pancreas [153]. Other studies have not observed hepatic oxidative stress in response to high-sucrose or high-fructose diets (based on liver glutathione content, lipid peroxidation products, liver thiobarbituric acid–reactive substances) [123,153,154]. Finally, provision of a high-fructose diet (57% of carbohydrates as fructose) in the absence or presence of 3.4 g of vitamin E per kilogram of diet resulted in a 42% improvement in whole body insulin action (based on the glucose infusion rate during a glucose clamp). However, whole body insulin action in the vitamin E–supplemented group was still significantly reduced (glucose infusion rate was 84 ± 8 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) when compared with a control group not receiving fructose (glucose infusion rate was 172 ± 10 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) [155].

11. Biologic modifiers of the adaptive response to sucrose and fructose

Female Wistar rats, unlike their male counterparts, do not develop insulin resistance nor accumulate lipid in plasma or liver in response to a high-sucrose diet provided for up to 8 weeks [156]. Subsequent studies have reported a delay in the development of hypertension [157] and protection against sucrose-induced oxidative stress in the heart [153,157] in female rats. Estrogens, via their effects on antioxidant capacity, may contribute to this protection [153].

Age-related variability in the hyperlipidemic effects of fructose added to the drinking water of rats was demonstrated as early as in 1970. When male Sprague-Dawley rats were provided high glucose, sucrose, fructose, or fructose + glucose (70% by weight) for 2 to 3 weeks, circulating triglycerides were not increased in weanling rats but were increased in mature animals (~500 g body weight) when compared with glucose- or starch-fed controls [158]. This variability was investigated further using male, Wistar rats that were either 2 or 12 months old upon initiation of either a high-starch (68%) or a high-fructose (40%) diet for 3 weeks [87]. In this study, plasma triglycerides were increased more in younger rats but liver triglycerides were increased more in older rats. Older rats were characterized by lower rates of

hepatic triglyceride secretion and an impaired stimulation of apolipoprotein B gene expression. In addition to age-related variability in fructose- and sucrose-mediated effects on triglyceride levels, a previous study also observed greater effects of dietary sucrose on glucose-stimulated insulin secretion in 26-month-old Fisher 344 rats compared with 6- or 12-month-old animals [159].

12. Genetic factors and the adaptive response to sucrose and fructose

The genetic susceptibility to metabolic disorders induced by a high-fructose diet was recently investigated in 10 strains of mice [160]. Mice were provided either a control, high-carbohydrate diet (58% carbohydrate with no fructose) or a high-fructose diet (66% fructose) for 8 weeks and were studied after a 2-hour fast from their respective diets. The high-fructose diet induced postprandial hyperinsulinemia, hypertriglyceridemia, and visceral fat accumulation in CBA/JN, C3H/He, and BALB/c mice. In mice from the DBA/2N, DBA/1JN, and C57BL/6N strains, these responses were either absent or blunted. The hepatic expression of the sterol regulatory element-binding protein 1 (SREBP-1), a key transcription factor for hepatic expression of lipogenic enzymes, was increased in CBA/JN, C3H/He, and BALB/c. DBA/2N mice were characterized by a single nucleotide mutation (guanine to adenine) at −468 base pairs from the putative starting point of the SREBP-1 gene. These data suggest that polymorphisms in the SREBP-1 gene may be a determinant of susceptibility to high-fructose diet–induced metabolic perturbations.

Stearoyl-CoA desaturase (SCD) is a microsomal, rate-limiting enzyme in the biosynthesis of mono-unsaturated fatty acids. When a high-fructose diet (60% fructose) was provided to SCD −/− mice (pure 129 SV background), fructose failed to induce SREBP-1 or lipogenic genes. These data suggest that SCD gene expression is necessary for fructose-mediated induction of lipogenic gene expression in mice. As was discussed previously, female rats appear to be protected from a number of sucrose- and fructose-induced metabolic abnormalities. In a recent study, increased expression of CD36 mRNA was observed in livers taken from female vs male rats [161]. Interestingly, this sex-related difference in the level of hepatic CD36 gene expression was also observed in humans [161]. CD36 is an integral membrane glycoprotein found on the surface of a variety of cells and has an important role as a facilitator of membrane fatty acid transport [162]. The phenotype of CD36-null mice includes hypoglycemia, hypoinsulinemia, and enhanced insulin sensitivity compared with wild-type mice. However, CD36-null mice are more responsive to fructose-induced impairments in insulin action when compared with wild-type mice [162]. In addition, a single nucleotide polymorphism (−468 G to A) at the promoter region of SREBP-1c appears to be associated with an impairment in the ability of fructose to induce hepatic lipogenesis [160]. Thus, the adaptive response to sucrose and fructose may be determined, in part, by specific genetic traits [80].

13. Application to humans

High-fructose corn syrup has become a favorite substitute for sucrose in carbonated beverages, baked goods, canned fruits, jams and jellies, and dairy products [8,9]. Sweet corn–based syrups were developed during the past 3 decades and now represent close to one half of the caloric sweeteners consumed in the United States [9,163]. Several recent reviews have suggested that the increased use of high-fructose corn syrup and refined carbohydrates (defined as sugars added to a food and includes sweeteners such as sucrose, high-fructose corn syrup, honey, molasses, and other syrups) may contribute to the current obesity and type 2 diabetes epidemics [9,25,164]. In women, a statistically significant positive relationship was demonstrated between fructose and the risk for colorectal cancer [165]. However, direct, experimental evidence demonstrating a causal relationship between sucrose or fructose and metabolic parameters (eg, insulin resistance, body fat accumulation, dysregulation of lipid or carbohydrate metabolism) associated with obesity and type 2 diabetes in humans is lacking.

There are at least 3 human studies that have reported increased weight gain in human subjects in response to added fructose or sucrose [166-168]. In all of these studies, ad libitum energy intake was increased when fructose or sucrose was provided as a supplement to the diet. These data are consistent with the notion that increased access to high-fructose corn syrup and/or sucrose-containing beverages may contribute to the obesity epidemic via provision of excess energy and, therefore, promotion of positive energy balance [9]. In contrast, epidemiologic studies have typically found an inverse relationship between the intake of sucrose and body weight in adults and children [169-171]. The long-term, multicenter Carbohydrate Ratio Manipulation in European National Diets (CARMEN) trial, in which a diet low in fat and high in simple sugars, consumed ad libitum for 6 months, resulted in reduced body weight and fat mass in overweight subjects [172]. Recent evidence from Poppitt et al [173] supports the results from the CARMEN trial.

In contrast to the relatively consistent negative effects (eg, insulin resistance, hypertriglyceridemia) of high-sucrose and high-fructose diets in rats, most clinical human studies have not observed significant effects of dietary sucrose or fructose on parameters related to insulin action, lipid profiles, or other cardiovascular disease risk factors, such as hypertension [174-181]. However, sucrose-mediated effects on glucose tolerance and lipid parameters, such as total and very low-density lipoprotein triglyceride, have been observed in human populations that were defined as carbohydrate-sensitive, hyperinsulinemic, or hypertriglyceridemic [92,182].

In most cases, animal studies have used diets enriched in sucrose (32%-69% of energy) or fructose (35%-88% of

energy) [82,83,88,93-95,97,98,100,101,104,107]. Although it should be noted that a relatively low-sucrose diet (18% of energy as sucrose) can induce insulin resistance that is primarily localized to the liver in rats. However, the induction of hepatic insulin resistance in response to the low-sucrose diet required more than 16 weeks to become manifest [71]. In contrast, most "long-term" (>1 day) human studies typically have used amounts of sucrose ranging from 5% to 40% of total energy [92,168,174-180], although at least 1 study used a diet that contained 80% sucrose [176]. Thus, whether and to what extent current dietary intakes of sucrose and fructose have contributed to the obesity and type 2 diabetes epidemics and/or metabolic perturbations associated with these diseases are uncertain [80,183,184].

14. Perspective

Fructose is an intriguing nutrient because of its selective hepatic metabolism [11]. The annual per capita consumption of extrinsic or added fructose has increased from ~0.2 kg in 1970 to ~28 kg in 1997 [25,185]. This increased consumption has been linked, by some but not all studies, to the increased prevalence of obesity and type 2 diabetes in the United States [9,25,80,164,167,170,178,183,186]. The liver is exquisitely sensitive to changes in nutrient delivery and is uniquely suited to metabolize ingested simples sugars, such as fructose and glucose [11,22,146]. Predictably, high intakes of fructose or sucrose lead to rapid adjustments in liver metabolism. These adjustments include modulation of hepatic insulin action.

Organisms reprogram metabolic pathways to adapt to changes in nutrient availability, hormonal milieu, and energy demands. This requires that stimuli are sensed and highly specific responses engaged. Mitogen-activated kinases link a variety of extracellular signals to a diverse range of cellular responses [120]. The stress-activated protein kinases, principally the JNK, are activated by cell stress–inducing stimuli [187]. We hypothesize that fructose, at high rates of delivery, provokes an hepatic stress response involving activation of JNK and subsequent reduced hepatic insulin signaling [70]. The signal for activation of JNK is presently unknown, but may involve hepatic intermediates such as xylulose 5-phosphate, diacylglycerol, Pi, and/or methylglyoxal. The extent to which these hepatic adaptations occur in humans will likely depend on the concentration of fructose presented to the liver, the duration of exposure to increased fructose delivery, as well as multiple biologic and genetic factors.

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