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Review

Fructose: a highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and the metabolic syndrome

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Dekker MJ, Su Q, Baker C, Rutledge AC, Adeli K. Fructose: a highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and metabolic syndrome. *Am J Physiol Endocrinol Metab* 299: E685–E694, 2010. First published September 7, 2010; doi:10.1152/ajpendo.00283.2010.—As dietary exposure to fructose has increased over the past 40 years, there is growing concern that high fructose consumption in humans may be in part responsible for the rising incidence of obesity worldwide. Obesity is associated with a host of metabolic challenges, collectively termed the metabolic syndrome. Fructose is a highly lipogenic sugar that has profound metabolic effects in the liver and has been associated with many of the components of the metabolic syndrome (insulin resistance, elevated waist circumference, dyslipidemia, and hypertension). Recent evidence has also uncovered effects of fructose in other tissues, including adipose tissue, the brain, and the gastrointestinal system, that may provide new insight into the metabolic consequences of high-fructose diets. Fructose feeding has now been shown to alter gene expression patterns (such as peroxisome proliferator-activated receptor-γ coactivator-1α/β in the liver), alter satiety factors in the brain, increase inflammation, reactive oxygen species, and portal endotoxin concentrations via Toll-like receptors, and induce leptin resistance. This review highlights recent findings in fructose feeding studies in both human and animal models with a focus on the molecular and biochemical mechanisms that underlie the development of insulin resistance, hepatic steatosis, and the metabolic syndrome.

hyperlipidemia; inflammation; gene expression; triglyceride; intestine

AS THE GLOBAL INCIDENCE OF OBESITY continues to increase, the search to identify the dietary components that contribute to this phenomenon is intense and ongoing. A controversial topic to be sure, fructose has garnered considerable attention in the last decade or so as a possible contributor to this worldwide rise in overweight and obesity rates (131). In addition to contributing to the caloric overconsumption and the associated energy imbalance that are currently rampant in developed countries, the unique metabolism of fructose may hold intriguing insight into why fructose has been implicated in the etiology of a number of metabolic diseases (22, 126). It is, of course, important to note that the human diet rarely (if ever) encounters fructose as a single nutrient. In most cases, the dietary exposure to fructose comes through the coingestion of glucose via sucrose (glucose and fructose) or industrial blends of fructose and glucose (high-fructose corn syrup, HFCS) in ratios very similar to sucrose (50% fructose, 50% glucose). There is a large amount of interest in the metabolic syndrome (MetS), the collection of obesity-related risk factors associated with insulin resistance (32), in experimental and clinical obesity research. Initially, fructose drew great interest as a potentially beneficial sweetener for patients with diabetes mellitus due to its much lower glycemic index compared with glucose (14, 60). An additional characteristic of fructose that might have been well suited for diabetic patients is that fructose does not stimulate insulin secretion or require insulin for the initial steps of its hepatic metabolism. Following glycolysis to pyruvate, fructose carbon is a substrate for pyruvate dehydrogenase (PDH), an enzyme metabolically regulated by insulin. As insulin secretion is not stimulated by fructose, substantial amounts of fructose are anaerobically metabolized to lactate (1, 132). However, fructose has been cast in a much more pejorative light in recent years.

The contribution of fructose (and particularly HFCS) to the increased incidences of obesity and the MetS is under considerable scrutiny and is hotly debated. Critical evaluations of the literature have emerging as being both for (35) and against (42) dietary restriction. It is important to note that, in many of the studies outlining the biological pathways of fructose, high levels of pure fructose (60% of diet) have been utilized. The outcomes observed are not necessarily applicable to the amount of fructose currently encountered in the human diet, particularly that fructose is typically consumed concomitantly with glucose. Nonetheless, fructose consumption in human subjects has been linked to each of the MetS identifying features, which include dyslipidemia (69, 126), visceral adiposity (126), insulin resistance (126), and high blood pressure (for an extensive review, see Ref. 131). Although calorically

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identical to glucose, fructose metabolism (hepatic metabolism in particular) differs from that of glucose in several important ways. The rate of hepatic uptake of fructose from portal circulation is greater than the rate of glucose uptake, and because fructose metabolism bypasses phosphofructokinase, fructose metabolism is not under the regulatory control of insulin (140). An underinvestigated aspect of fructose is the possibility that glucose, when consumed along with fructose, may facilitate fructose uptake and vice versa, as suggested by plasma glucose excursions measured during the consumption of glucose-fructose-, sucrose-, and HFCS-sweetened beverages (124). As lipids are strongly linked to the development of obesity and insulin resistance (2, 21, 33), the prevailing hypotheses concerning the mechanisms by which fructose promotes MetS focus on the lipogenic nature of the sugar. The induction of lipogenesis would increase deposition of triglyceride (TG) in adipose tissue (obesity) and ectopic tissues such as liver (hepatic steatosis) and muscle, eventually resulting in impaired insulin signaling and dyslipidemia (125). Fructose feeding has therefore been historically utilized as a model for studying various aspects of hepatic dyslipidemia and insulin resistance (6, 13). The results of a recent study suggest that fructose consumption may specifically promote lipid deposition in visceral adipose tissue, particularly in men, whereas glucose consumption appears to favor lipid deposition in subcutaneous adipose tissue (126). Interestingly, 24-hour plasma TG profiles are increased to a greater extent following the consumption of fructose- and HFCS-sweetened beverages compared with glucose consumption (124). This suggests that the coingestion of fructose with glucose may also elicit an unfavorable TG profile similar to that of fructose alone. Although lipogenesis is certainly at the core of the biochemical changes induced by fructose, emerging evidence suggests that the simultaneous stimulation of alternate physiological and signaling pathways may also contribute to the deleterious effects of fructose (Fig. 1). The goals of this review are to highlight emerging concepts in fructose metabolism, link these concepts to current knowledge of MetS, and identify the truly exciting areas with substantial research potential.

Fructose Takes Aim at the Liver

The liver is an essential organ for the maintenance of lipid, glucose, and hormonal homeostasis. As such, the liver is at the crossroads of metabolic health and disease. Since the identification of sterol regulatory element-binding proteins (SREBPs) by Brown's and Goldstein's groups as transcription factors that modulate lipid homeostasis (59, 145), there has been a considerable focus on gene expression in the regulation of intracellular carbohydrate and lipid concentrations. Fructose may activate SREBP-1c independently of insulin, which activates genes involved in de novo lipogenesis (DNL) (38, 81, 93). When glucose is replaced with fructose, carbohydrate regulatory element-binding protein (ChREBP) activity and nuclear SREBP-1 are increased following two weeks of dietary treatment (66). Prolonged consumption of fructose, but not glucose, also increased hepatic fractional DNL in humans when measured during energy-balanced feeding (126). The increased rate of fructose-induced DNL generates fatty acids that can then be incorporated into hepatic TG or other lipid species. Increased hepatic lipid levels are associated with increased very-low-density lipoprotein (VLDL) synthesis and secretion, specifically that of VLDL1 (4). Apolipoprotein B-100 (apoB) is essential for the intracellular assembly of TG into VLDL, and apoB degradation is reduced when hepatic lipid is increased (100), which leads to the accumulation of apoB in the hepatic endoplasmic reticulum (ER) and causes ER stress (130). Recent experimental evidence has demonstrated that ER stress

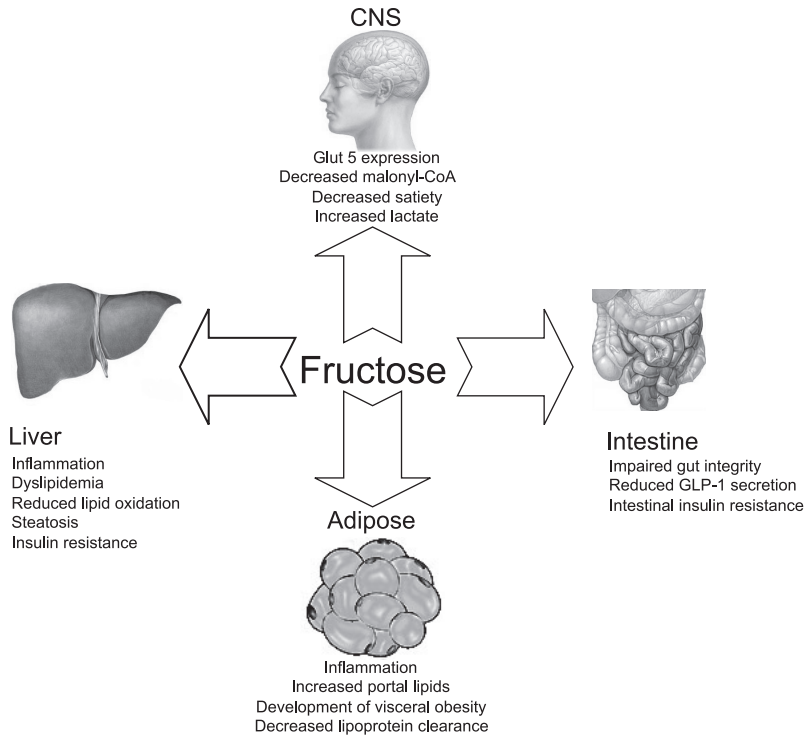

Fig. 1. Whole body effects of chronic fructose consumption. Disturbances occur in multiple tissues, including liver, adipose, the gastrointestinal system, and the central nervous system, following chronic fructose consumption. This constellation of abnormalities influences multiple aspects of the metabolic syndrome, including dyslipidemia, insulin resistance, and central adiposity. Additional emerging complications, such as impaired satiety, increased hepatic lipid deposition, inflammation, and altered gastrointestinal integrity may be mechanistically responsible for the clinical alterations observed with fructose consumption [images taken from ADAM Education (http://adameducation.com)].

promotes SREBP-1c activation and thus contributes to DNL (63, 130). Reduction of ER stress markers, via overexpression of chaperone glucose-regulated protein-78 (GRP78) in the livers of *ob/ob* mice, inhibited SREBP-1c cleavage and the expression of SREBP-1c and SREBP-2 target genes. Furthermore, hepatic TG and cholesterol levels were reduced and insulin sensitivity improved in GRP78-injected mice (63).

Fructose feeding has also been shown to induce the activation of ChREBP and increase the expression of lipogenic genes such as fatty acid synthase (FAS), acyl coenzyme-A carboxylase (ACC), and stearoyl coenzyme-A desaturase-1 (108). Interestingly, statin treatment in fructose-fed rats with statin (atorvastatin) completely attenuated fructose-induced increases in circulating TG and free fatty acids (FFA) and normalized elevated blood pressure (108). This may be due to activation of protein kinase A (PKA) by atorvastatin, resulting in the sequestering of ChREBP away from the nucleus, and the activation of carnitine palmitoyltransferase (CPT I) (108). The net result of PKA activation by statin treatment could therefore be seen to promote the oxidation of fatty acids over synthesis and storage of TG, resulting in decreased steatosis and lipid intermediates and enhanced insulin signaling (108).

Central abdominal obesity (as measured by waist circumference) is a core feature of the MetS (95). Under experimental conditions, human consumption of beverages containing fructose, rather than glucose, was associated with increased visceral obesity (126). In humans and rodents, mesenteric adipose tissue is the visceral adipose tissue depot that is situated in an important anatomic location to participate in the portal drainage of the gastrointestinal system. Thus, during periods of caloric excess, disturbances in this adipose tissue depot such as increased lipolysis of endogenous lipid stores would contribute to the delivery of FFA (97) and inflammatory mediators (41) directly to the liver. Collectively, this has been termed the portal theory of insulin resistance (16, 31). Metabolically, mesenteric fat has a high rate of lipolysis and low response to the inhibition of lipolysis by insulin (91). In fact, dysfunction in lipolysis and expression of lipolytic genes have been demonstrated in obese diabetic subjects (144).

It has been suggested that fructose consumption promotes development of MetS through increased adiposity and insulin resistance in adipose tissue, which lead to increased circulating and portal levels of FFA (111). The resultant increase in hepatic FFA uptake increases hepatic lipid availability and promotes hepatic insulin resistance (16). However, Stanhope et al. (126) recently demonstrated that human subjects consuming fructose had significantly higher rates of hepatic DNL than those consuming glucose, accompanied by an elevated 23-hour postprandial TG level, altered lipid profile, lipoprotein remodeling, and decreased insulin sensitivity, while they maintained similar concentrations of circulating FFA. The absence of an effect of fructose on systemic FFA suggests that fructose may promote insulin resistance by providing a more direct source of intrahepatic lipid via DNL (125). It is important to note that FFA are not the only biologically relevant product of adipose tissue, as will be discussed later. Hepatic DNL limits fatty acid oxidation in the liver via production of malonyl coenzyme-A, which reduces the entry of fatty acids into the mitochondria (82) by inhibiting CPT I. Thus, fructose-induced DNL may increase hepatic lipid by supplying endogenous fatty acids. Taken together, the increased visceral adiposity and DNL observed with fructose feeding likely create a scenario ideal for lipid overloading, leading to impaired insulin sensitivity and hyperlipidemia.

Fructose-Induced Disturbances in Circulating Lipid and Lipoprotein Clearance

The significantly lower postprandial postheparin lipoprotein lipase (LPL) activity in subjects consuming fructose suggested that reduced TG clearance also contributes to fructose-induced postprandial hypertriglyceridemia (126). Both reduced postprandial exposure to insulin (132) and decreased insulin sensitivity (83) have likely contributed to a lowered postprandial LPL activity in subjects consuming fructose compared with those consuming glucose (126). Subcutaneous adipose tissue is more sensitive to the effects of insulin in activating LPL than visceral adipose tissue (44); thus, the differential LPL responses may direct fat deposition toward subcutaneous adipose tissue following glucose consumption and toward visceral adipose tissue following fructose exposure (126). Apolipoprotein CIII (apoCIII) is an inhibitor of LPL and hepatic lipase and plays a pivotal role in the hydrolysis and clearance of TG-rich particles such as VLDL and chylomicrons (117). In vivo studies with high-fructose feeding of hamsters demonstrated that fructose stimulated forkhead box O1 (FOXO1) production and promoted its nuclear redistribution in liver (130). This, in turn, augmented apoCIII production and impaired TG hydrolysis (130), highlighting a possible mechanism for impaired hepatic TG-rich lipoprotein clearance following fructose feeding.

North Americans typically spend 18 hours each day in what is known as the postprandial period (47). Elevated postprandial TG concentrations have been increasingly associated with proatherogenic conditions (12, 61, 78, 98, 123). This link may be due to lipoprotein remodeling induced by increased levels of VLDL1 and mediated by cholesteryl ester transfer protein and hepatic lipase, which results in increased concentrations of small dense low-density lipoproteins (LDL) and remnant-like lipoproteins (3, 17, 67, 80, 101). Small dense LDL particles are more easily oxidized than larger LDL particles (102); accordingly, subjects consuming fructose also have been shown to have significantly increased concentrations of oxidized LDL. Fructose induced a remarkable doubling in both fasting and postprandial small dense LDL concentrations in subjects with MetS compared with non-MetS subjects, which suggests that preexisting hypertriglyceridemia can exacerbate fructose-induced lipoprotein remodeling (126).

Role Of β-Oxidation and Inflammatory Signaling in Fructose-Induced Insulin Resistance

Peroxisome proliferator-activated receptor (PPAR)γ coactivator-1β (PGC-1β) has been reported to coactivate its partners through augmentation of their transcriptional activity (76). Though initially described to pair with PPARγ, the number of partners for PGC-1 transcription factors is rapidly growing. Utilization of a PGC-1β antisense oligonucleotide (ASO) to knock down the expression of PGC-1β has been shown to improve the metabolic phenotype induced by fructose feeding by reducing expression of SREBP-1 and downstream lipogenic genes in the liver. PGC-1β ASO treatment reversed hepatic insulin resistance induced by fructose in both basal and insulin-

stimulated states (94). This important study identified differential effects of PGC-1β ASO on the liver in regular-chow-fed rats and high-fructose-fed rats. In regular-chow-fed rats, PGC-1β ASO induced slight but statistically significant reductions in the sensitivity of hepatic glucose production to the suppressive effects of insulin (94). The reduced insulin sensitivity was due to decreased mitochondrial fatty acid oxidation and the accumulation of hepatic diacylglycerol (DAG), which in turn inhibited insulin signaling via activation of protein kinase Cξ (114). Metabolism in high-fat diet-fed rats was unaffected when treated with the same PGC-1β ASO (94). This evidence suggests that fructose may modulate many of its metabolic effects, including stimulation of DNL, via activation of specific metabolic targets by PGC-1β.

PGC-1α and -β have been reported to coactivate both PPARα and nuclear respiratory factor (NRF)-1 (115). PPARα plays a key role in the transcriptional control of genes encoding mitochondrial fatty acid oxidation enzymes such as long-chain acyl coenzyme-A dehydrogenase and medium-chain acyl coenzyme-A dehydrogenase. Fructose administration (10% wt/vol) in the drinking water of rats reduced the transactivating and transrepressing activity of PPARα (109). The mRNA levels of PPARα target genes, such as CPT I (51) and PPARα itself (45), were decreased as a result of the reduced transcriptional activity of PPARα. Decreased PPARα activity compromises fatty acid oxidation in mitochondria, a catabolic process directly controlled by CPT I (51). The accumulation of FFA in liver may then induce oxidative stress (109). The same study also observed an increased activity of proinflammatory transcription factor nuclear factor-κB (NF-κB). These changes were not observed in rats given glucose in their drinking water. The leptin-signal transducer and activator of transcription-3 pathway may be involved in this regulation (109).

Extrahepatic Effects of Fructose Feeding

In addition to well-characterized hepatic effects of fructose feeding (such as steatosis, increased lipoprotein secretion, hepatic insulin resistance), fructose has been identified to alter biological pathways in several extrahepatic tissues, including the central nervous system, adipose tissue, and the gut. These new areas of research have expanded the physiological role of high-fructose diets and now introduce a whole body approach to investigating the metabolic fate of fructose.

Central Effects of Fructose

The role of insulin resistance in neuronal dysfunction has been well documented, and the observation that fructose can induce these changes is also now well documented. Several studies have linked insulin resistance and type 2 diabetes to deficits in hippocampal declarative memory (28, 86, 128), and Stranahan et al. (129) have shown that mice on hypercaloric diets have impaired memory, reduced dendritic spine density, and impaired long-term potentiation. When fructose-specific neuronal effects are evaluated, fructose-fed rats and hamsters show hippocampal insulin resistance associated with impaired memory retention and decreased long-term depression formation in hippocampal neurons (87, 110). These effects are likely the result of systemic insulin resistance, as insulin is known to play a key role in neuronal synaptic plasticity (96).

The effects of fructose on the central nervous system may be more far reaching than its ability to elicit insulin resistance. Recent studies have shown a more direct effect of fructose on the brain and in the general function of neurons. The fructose transporter GLUT5 showed increased mRNA expression in brains of fructose-fed rats, accompanied by increased protein levels of GLUT5 in the hippocampus (120), implying that neuronal fructose uptake can be increased with fructose feeding. Lindqvist et al. (77) have reported increased ghrelin as well as leptin levels in fructose-fed rats. Increased circulating leptin may relate to development of leptin resistance upon high-fructose feeding (118). This would imply that despite increases in leptin levels there is a decreased ability to respond to leptin, leading to decreased satiety. This observation implies the potential for increased food intake with fructose feeding. It should be noted, however, that the changes in ghrelin and leptin are not excusive to the one sugar, as both glucose and sucrose overconsumption elicited similar increases in both leptin and ghrelin. In addition to these observations, central administration of fructose can cause increased appetite as well as significant changes in neuronal function. Hyperphysiological doses of fructose administered directly to the brain have been shown to induce increased feeding, whereas glucose causes a decrease in food consumption (89). This was found to be associated with differential induction of malonyl-CoA between the two sugars. Malonyl-CoA is known to cause an anorectic effect, which leads to the loss of appetite. Glucose administration in the brain activates the glycolytic cycle, which leads to increased neuronal ATP levels; this is associated with a fall in AMP levels. Since AMP is an activator of AMP kinase (AMPK), there is a decrease in AMPK phosphorylation/activity. AMPK activity, in turn, catalyzes the phosphorylation/activation of acetyl-CoA carboxylase (ACC), glucose blocks this activation and this leads to increased malonyl-CoA and decreased food intake. Fructose administered centrally decreases ATP levels and leads to a subsequent decrease in hypothalamic malonyl-CoA levels (27, 143). This is thought to lead to a decrease in satiety. In contrast to the above observations, fructose given as a pre-meal load showed no difference in food intake compared with either glucose or sucrose pre-meal loads (5), and all three sugars, when given to rats in drinking water, showed the same effects on food consumption (77).

While direct central administration of fructose may not be a typical physiological condition, as dietary fructose is rapidly taken up and metabolized by the liver, the signaling changes induced by fructose are intriguing and may point to larger systemic signaling changes that could lead to alterations in satiety factors. For example, fructose feeding has a well-documented effect of dramatically increasing hepatic lactate production (1, 132). As neurons utilize lactate as well as glucose as energy substrates, increased lactate and reduced insulin responses seem likely signals from the periphery to the brain conveying metabolic status following fructose intake.

Evidence for Fructose-Induced Leptin Resistance

Leptin is a well-characterized adipose-derived hormone with central and peripheral effects on food intake and dietary substrate handling (for review, see Ref. 20). Leptin receptor knockout mice (*db/db*) and mice that secrete mutant leptin

peptides (*ob/ob*) are well characterized for a phenotype that includes obesity, hepatic steatosis, and insulin resistance (146). Leptin stimulates fatty acid oxidation through the activation of PPARα (71) through the action of AMPK (90). However, obese human subjects (116) and diet-induced obese mice (43) and rats (141) demonstrate resistance to leptin, which has been thought to contribute to lipid deposition in the liver (71) and skeletal muscle (127). Acutely, fructose feeding decreases leptin secretion in human subjects (132). As insulin-mediated glucose metabolism has been shown to regulate leptin release (92), this phenomenon can likely be attributed to a lack of insulin response with fructose consumption. Importantly, four weeks of fructose feeding induced hyperleptinemia in humans (68). Along with decreased insulin sensitivity, hepatic steatosis, and increased circulating TG, rats fed fructose also exhibited hyperleptinemia (75, 109, 138), making the fructose-fed rat a useful tool for studying leptin resistance. These apparently conflicting responses appear to reflect a difference in acute vs. chronic exposure to fructose, where the development of leptin resistance and hyperleptinemia is likely due to increased adipose tissue mass induced by fructose feeding (54). The major pathway proposed to be responsible for leptin resistance involves the signaling molecule suppressor of cytokine signaling 3 (SOCS3). Fructose feeding induced SOCS3 expression and impaired serine/threonine phosphorylation, resulting in leptin resistance (75, 138). In addition, fructose can stimulate the expression of protein tyrosine phosphatase-1B (75). Vila et al. (138) observed that rats fed fructose exhibited impaired c-Jun NH_2-terminal kinase (JNK) and mitogen-activated protein kinase signaling and increased expression of FOXO1 due to SOCS3 expression. In turn, this led to decreased PPARα, suggestive of impaired fatty acid oxidation, which would contribute to TG accumulation in the liver. Conversely, the activation of PPARα reversed leptin resistance in fructose-fed rats (75). Fructose feeding also increased hepatic ceramide concentrations, leading Vila et al. to suggest that incomplete fatty acid oxidation due to PPARα impairments provided substrate for ceramide synthesis (138). This could also lead to activation of protein phosphatase-2A and thus contribute to deficiencies in leptin signaling and exacerbate metabolic disease (138). Although hyperleptinemia may be a result of increased adipose tissue mass, it appears that leptin resistance precedes increased adiposity, elevated circulating leptin, and changes in glucose metabolism in rats (118), which suggests that leptin resistance may be an early hallmark of fructose feeding-induced metabolic dysfunction.

Fructose-Induced Inflammation

Low-grade inflammation is now recognized as a common feature of the metabolic abnormalities observed in obesity (31, 56, 107). TNFα is increased in obesity and has been extensively characterized for its role in insulin resistance (36, 135). The discoveries that increased adipose-derived TNFα in obesity contributed to insulin resistance (57) and that a lack of functional TNFα protected obese mice from diet-induced insulin resistance (137) have stimulated substantial research in diabetes and insulin resistance. Increased plasma concentrations of TNFα have been observed following fructose feeding in mice (122) and hamsters (136). Furthermore, TNFα mRNA was increased in hepatic tissues in fructose-fed mice (53, 122).

The activation of inflammatory pathways by fructose feeding can have a direct influence on hepatic and intestinal secretion of lipoproteins. Classical inflammatory pathways, such as NF-κB, are increased with fructose feeding (109) and contribute to hepatic TG overproduction (136). To determine the mechanism that underlies the dyslipidemic properties of TNFα, recent studies in our laboratory examined the effect of TNFα infusion on lipoprotein and TG production from both hepatic (103) and intestinal sources (104). In the liver, TNFα infusion led to decreased tyrosine phosphorylation of the insulin receptor and insulin signaling molecules insulin receptor substrate-1 (IRS-1) and Akt upon insulin stimulation, indicating decreased insulin sensitivity. These changes accompanied the increased production of VLDL1-type particles (103). Similarly, TNFα infusion decreased tyrosine phosphorylation of insulin receptor, IRS-1, and Akt in the intestine, leading to increased production of apoB48-containing chylomicron particles (104). In both cases, decreased insulin sensitivity was accompanied by increased mass and expression of microsomal TG transfer protein, a key protein involved in the maturation and lipid loading of TG-rich lipoproteins (103, 104).

Free radicals generated from increased oxidative stress are linked to insulin resistance (37). It is perhaps not surprising, then, that fructose feeding has been shown to increase oxidative stress (30) and is associated with MetS in rodents, as reviewed previously (88). Although not a substantial focus of this review, fructose feeding in rats has been shown to increase hydrogen peroxide generation and inflammatory markers (99), associating fructose feeding with an additional emerging factor associated with insulin resistance. Perhaps more convincing of the direct effects of fructose on oxidative stress is the observation that treatment of fructose-fed rats with antioxidants decreased reactive oxygen species generation and prevented insulin resistance (10, 121). Oxidative stress and inflammation converge in shared pathways connected to insulin resistance, such as JNK1, making both stimuli important factors to consider with fructose exposure.

Toll-like receptors (TLR) are important pattern recognition receptors in the immune system that identify bacterial pathogens (for review, see Ref. 70). First identified in *Drosophila* (7), a human analog of Toll (TLR-4, also present in rodents) has also been described (84). TLR-4 recognizes lipopolysaccaride (LPS) residues from endotoxic bacteria and activates the inflammatory NF-κB pathway. Additional endogenous ligands for TLR-4, such as ceramide (40) and FFA (119), have now been identified. Importantly, increased TLR-4 expression has been associated with insulin resistance (106). TLR-4 knockout mice have been shown to be resistant to the impaired insulin sensitivity induced by lipid infusion and are partially resistant to the negative effects of a high-fat diet (119). Thus, it appears that TLR-4 is at the crossroads of insulin resistance, lipids, and inflammation (119). Recently, Spruss et al. (122) demonstrated that TLR-4 knockout mice were resistant to fructose-induced liver steatosis. Although fructose-fed wild-type mice exhibited markedly increased portal LPS and MyD88 (a marker of TLR-4 signaling), TLR-4 knockout mice fed fructose demonstrated levels similar to those of control mice. In the liver, TNFα mRNA expression and insulin resistance were induced in fructose-fed wild-type mice but not in TLR-4 knockout mice. The authors suggest that reductions in gut integrity were responsible for an influx of gastrointestinal

microbiota and increased LPS concentration (23, 25). This hypothesis is strengthened by the findings that nonabsorbable antibiotic treatment of mice consuming fructose prevented fructose-induced increases in LPS, hepatic lipids, and hepatic TG (15). Changes in gut microbiota are increasingly being linked to obesity and the metabolic syndrome (for review, see Refs. 26 and 74). As this is a rapidly expanding area of research, future investigation into the role that fructose may have in microbiota health and species colonization should provide intriguing results. Although the traditional concept of fructose-induced metabolic dysregulation has focused on lipogenesis and insulin regulation, these data demonstrate an alternate method by which fructose induces insulin resistance, through increased bacterial induction of an inflammatory response accompanied by steatosis.

Finally, although there is a dramatic increase in hepatic TG following fructose feeding, it is now well established that TG per se are not responsible for the deleterious effects of hepatic steatosis but that the accumulation of lipid species such as DAG (114) and ceramide (55, 113) impair insulin signaling and may induce inflammation. Although much of these data were derived from high-fat feeding studies, Vila et al. (138) have recently demonstrated that ceramides are significantly increased in the livers of fructose-fed rats. As has already been discussed, fructose is a potent lipogenic stimulus in the liver. The study of lipid intermediates is an emerging area of research, and more directed studies are required to unravel a possible role for fructose.

Role of the Gut in Meditating the Fructose Response

Increased lipoprotein secretion associated with intestinal insulin resistance has been identified as a factor strongly associated with aspects of MetS, including central adiposity (18, 19), insulin resistance (8, 9), and elevated fasting TG (29, 64). In fact, the gut may be a prime candidate for the convergence of many of the emerging factors involved in fructose-related disturbances. High-fructose feeding increased chylomicron production and secretion (52) and induced an insulin-resistant state characterized by impaired IRS-1 and Akt phosphorylation in the hamster small intestine (39). The administration of the PPARγ agonist rosiglitazone, an insulin sensitizer, reduced the effect of fructose feeding in hamsters (73). Interestingly, PPARγ agonist treatment may also increase body weight and body fat distribution from visceral to subcutaneous adipose tissue depots (142). Further study on metabolic consequences of PPARγ agonist treatment in MetS is required. As has been previously mentioned, infusion of TNFα increased the release of intestinal chylomicrons (104). Chylomicrons are known to promote the intestinal absorption of LPS (46); therefore, the increase in postprandial chylomicron levels in insulin resistance may expose LPS to the portal circulation (including mesenteric adipose tissue) and induce inflammation and insulin resistance. This inflammatory environment may propagate the secretion of TNFα, as has been seen following fructose feeding (122, 136), thus leading to enhanced chylomicron production and increased exposure to LPS, establishing a vicious cycle. Conversely, treatment of fructose-fed rats with the probiotic oligofructose, an oligosaccharide that has been suggested to promote intestinal integrity and inflammatory health (48, 72), blunted hepatic steatosis and circulating TG concentrations (24). Intestinal inflammation, absorption of LPS into circulation, and gastrointestinal integrity therefore represents potential contributors to the metabolic consequences of fructose consumption.

The gut actively secretes hormones that maintain gut integrity, modulate gastric emptying, and promote insulin secretion (34). Glucagon-like peptide-1 (GLP-1) is secreted in response to nutrient ingestion (133, 134, 139) and can abolish the postprandial rise in TG following infusion in human subjects (85). Consumption of a high-fructose beverage was associated with increased TG and prolonged GLP-1 release during a 24-hour period (132). However, others have observed a decreased GLP-1 response in human subjects following fructose ingestion compared with an equal amount of glucose (65). Recent evidence from our laboratory demonstrates a role for GLP-1 in the dyslipidemia observed following fructose feeding of hamsters (58). Pharmaceutical inhibition of dipeptidyl peptidase-4 (the enzyme responsible for GLP-1 breakdown) attenuated the fructose-induced rise in plasma TG, predominantly in the VLDL fraction (58). As the postprandial response to GLP-1 is blunted in obesity (105) and type 2 diabetes (79), the evidence from fructose feeding suggests that increased GLP-1 concentrations improve the metabolic response to a deleterious diet. Although these data are intriguing, very few studies have focused on fructose and gut hormone secretion. This makes it difficult to draw a conclusion regarding the particular effects of fructose, but it also represents an opportunity for further investigation into potential mechanisms of action.

Very recent evidence suggests that a single bolus of fructose initiates a positive regulatory control loop involving stimulation of leptin secretion and intestinal carbohydrate transport (112). During feeding, the stomach releases leptin (11), which enters the intestinal lumen (49, 50). Sakar et al. (112) demonstrated that oral fructose increased gastric juice leptin concentrations 15 minutes after gavage without altering circulating leptin concentrations. When leptin was given orally at a dose similar to the leptin concentrations in gastric juice following fructose ingestion, increased GLUT2 and GLUT5 transport activities and hepatic expression of SREBP-1c, ACC1, and FAS and activation of ACC1 in the liver were observed. Although these results have yet to be fully explained, they highlight a diverse and integrated regulatory system that is activated during the briefest of exposures to fructose. Taken together, the role of fructose in the gut offers new and exciting opportunities for future research and therapeutic target development.

Concluding Remarks

This review outlines several emerging molecular mechanisms and biochemical pathways that are stimulated following fructose exposure. High quantities of each food item would need to be consumed to achieve the dietary exposures represented in many of the rodent studies. However, as this review article clearly demonstrates, dietary exposure to fructose can potentially have substantial and profound metabolic consequences that possibly predispose individuals to chronic conditions such as type 2 diabetes and cardiovascular disease. A combination of exposure to fructose as a component of common sweeteners and increased caloric intake may, in fact, culminate in increased consumption of fructose. It is also

important to note that in many cases it is difficult to delineate between the effects of the fructose molecule and the impact of increased concentrations of endogenous lipids. Carefully controlled studies, such as the series of experiments by Nagai et al. (94), that utilize high-fat and -fructose diets can provide new and novel insight into the molecular impact of fructose intake. Additionally, many of the deleterious effects attributed to fructose via the consumption of sucrose and HFCS, particularly in sweetened beverages, may indeed be related to the consumption of excess calories, which has led the American Heart Association to recommend limiting added sugar intake in women to no more than 100 calories a day and men to no more than 150 calories a day (62). It is imperative that, in addition to in vivo and in vitro experiments, carefully designed dietary exposure and dose-response studies in human subjects with appropriate dietary controls (i.e., fat vs. glucose vs fructose) be completed to fully elucidate the metabolic consequences of fructose intake in humans.

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DISCLOSURES

The authors disclose no relevant financial or competing interests in the material presented herein.

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