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REVIEWS: CURRENT TOPICS

Fructose-mediated stress signaling in the liver: implications for hepatic insulin resistance

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Abstract

Organisms reprogram metabolic pathways to adapt to changes in nutrient availability. This requires that nutrient-based stimuli are sensed, signals are transmitted, and highly specific responses are engaged. We propose that in the liver, the mitogen-activated protein kinase, c-jun N-terminal kinase (JNK), links excessive nutrient metabolism with impaired insulin regulation of glucose production. The liver, by virtue of its anatomic position and selective regulatory features, buffers and is highly responsive to changes in nutrient delivery. In particular, sugars such as sucrose and fructose uniquely regulate and are selectively metabolized by the liver. We propose that when hepatic fructose uptake exceeds requirements for glycogen and energy (hepatic sugar excess), the JNK-signaling pathway is engaged as part of the adaptive response.

Keywords: Fructose; Liver; Obesity; Diabetes; Stress-activated protein kinases

1. Introduction

Obesity and type 2 diabetes are major public health problems [1–3]. Obesity increases one's risk of developing type 2 diabetes; in addition, both of these diseases lead to additional complications [3,4]. Thus, large efforts are currently in place to understand the etiology, prevention and treatment of these diseases. Although the causes of obesity and type 2 diabetes are complex, lifestyle changes can prevent or delay their onset. The Diabetes Prevention Program demonstrated that changes in diet and physical activity reduced the development of type 2 diabetes by 58% (National Diabetes Statistics, National Diabetes Information Clearinghouse, NIDDK).

Diet composition plays an important role in the development of obesity and type 2 diabetes [5]. The most publicized adverse attribute of diet composition relates to its role in body fat accumulation [6–8]. However, macronutrients also potently and directly influence glucose/lipid metabolism and insulin action. Acute infusions of lipids or fructose induce insulin resistance in both animals and humans [9–12]. Diets enriched with polyunsaturated fat, sucrose or fructose can lead to insulin resistance independent from increased energy intake and whole-body or visceral fat accumulation [13–16]. These data are consistent with a model in which diet composition can contribute to metabolic impairments associated with obesity and type 2 diabetes via direct effects on insulin action and indirectly through effects on fat mass and fat distribution.

Along with an increase in total energy consumption over the past few decades, there has been a shift in the types of nutrients consumed in the American diet [17]. The annual per capita consumption of extrinsic or added fructose has increased from ~0.2 kg in 1970 to ~28 kg in 1997. This increased consumption appears to mirror the increased prevalence of both obesity and type 2 diabetes in the United States [7,8,18]. We have proposed that impairments in the regulation of liver glucose metabolism are likely the earliest and most significant health consequences arising from these consumption patterns [19,20]. In this review, the rationale for such a proposal is discussed with a specific focus on fructose-mediated hepatic stress signaling. It should be noted that several other reviews discussing fructose-mediated effects in both animals and humans are available [8,19,21–27].

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1.1. The liver in obesity and type 2 diabetes

Obesity and type 2 diabetes are characterized by abnormalities in glucose and lipid metabolism, pancreatic insulin secretion and insulin action. Impairments in glucose production include a reduced ability of insulin to suppress glucose production (insulin resistance) and accelerated or inappropriate gluconeogenesis [28–31]. Type 2 diabetes is also characterized by overproduction of glucose and hyperglycemia [32]. Although the liver contributes significantly to these impairments, its quantitative contribution is difficult to assess since both the liver and kidney contribute to most in vivo measures of glucose production [33].

Impairments in liver glucose metabolism can contribute to the development of obesity and type 2 diabetes. For example, overexpression of phosphoenolpyruvate carboxykinase in mice produced a phenotype characterized by fasting hyperglycemia and hyperinsulinemia, impaired glucose tolerance and increased weight gain [34,35]. Overexpression of glucose-6-phosphatase (G6Pase) in rats resulted in impaired glucose tolerance and hyperinsulinemia [36]. Long-term overexpression of glucokinase in mice resulted in impaired glucose tolerance [37]. Finally, selective induction of hepatic insulin resistance increased weight gain in rats [38]. Thus, selective changes to insulin action or glucose metabolism in the liver can produce phenotypic changes similar to those that occur in obesity and type 2 diabetes.

1.2. Insulin action and the liver

Insulin has both direct (intrinsic effects that operate through the insulin receptor and signaling system of the hepatocyte) and indirect effects on glucose production. Indirect effects include the ability of insulin to suppress adipose tissue lipolysis and free fatty acid concentrations, insulin suppression of glucagon secretion and insulin signaling in the hypothalamus [33,39–41]. Adipose-tissue-secreted proteins can also regulate glucose production [42–45]. Direct and indirect effects of insulin function to reduce total glucose production and/or alter the relative contributions of glycogenolysis and gluconeogenesis to total glucose production [33].

The relative contributions of these direct and indirect actions on glucose production are an unresolved issue [32,46,47]. However, genetic approaches have reinforced the importance of direct insulin action. Liver-specific insulin receptor knockout mice exhibit insulin resistance, severe glucose intolerance and a failure to suppress glucose production and regulate hepatic gene expression [48]. In these mice, high-dose insulin infusion failed to suppress glucose production, indicating that both direct and indirect effects of insulin require an intact insulin-signaling pathway in the liver [49]. In addition, a recent study demonstrated that insulin receptor substrate (IRS)-2 was required for efficient insulin action in the liver [50]. We have hypothesized that the introduction of nutrients into the food supply, which are selective to and uniquely metabolized by the liver, impairs direct hepatic insulin action [12,19,51].

1.3. Hepatic sensitivity to nutrients and unique properties of fructose

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 specific to this organ. The portal vein receives the bulk of absorbed amino acids and simple sugars, is the liver's primary blood supply and is the site of pancreatic hormone and gastrointestinal peptide release [33]. Thus, the anatomic position of the liver places it in an important buffering position for nutrients and hormones [33,52].

Following ingestion of a meal containing complex carbohydrate or glucose, the liver becomes a glucose-consuming organ, accounting for 20–30% of the total dietary carbohydrate disposal [53,54]. Most of this glucose is used to replenish glycogen stores, with the remainder primarily directed to glycolysis [33,55]. The quantitative contribution of the liver to the disposal of dietary carbohydrate, however, is dramatically changed in the presence of fructose.

Sucrose, a disaccharide consisting of fructose and glucose, and fructose itself are targeted for hepatic metabolism. Fructokinase, the protein responsible for phosphorylation of fructose to fructose-1-phosphate, is expressed at highest concentrations in the liver [23,56]. Consequently, fructose extraction by the liver is exceptionally high [23]. In addition, fructose-1-phosphate stimulates glucose uptake in the liver [57,58]. These features predict that when complex carbohydrates or glucose is replaced by sucrose or fructose, the contribution of the liver to the disposal of dietary carbohydrate will be increased.

Current trends in postprandial carbohydrate consumption increase daily fructose load [7,8] and, therefore, the role of the liver in postprandial carbohydrate disposal. Increases in the fructose load to the liver, through diets enriched with sucrose or fructose or via portal vein fructose infusion, can alter the "normal" postprandial intrahepatic milieu [12,59–64]. We propose that these changes serve as signals of nutrient excess and elicit rapid responses that ultimately influence hepatic gene expression and insulin action.

2. Sucrose, fructose and the liver

We and others have used high-sucrose diets to investigate the immediate response of the liver to postprandial fructose exposure [19,61,65]. 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% of energy from sucrose, 12% corn oil and 20% casein (HSD) for 3 h to test the hypothesis that the presence of high fructose concentrations can induce a unique intrahepatic environment [61]. Despite similar energy intake, liver concentrations of xylulose 5-phosphate

(X5P), lactate and diacylglycerol were significantly increased, and inorganic phosphate (Pi) was significantly decreased in HSD compared with STD (Fig. 1). Notably, a diet containing 18% of energy as sucrose, 50% as corn starch, 12% as corn oil and 20% as casein elicited lower Pi (1.8±0.2 μmol/g liver) and higher X5P (36.2±3.9 nmol/g liver) after 3 h of refeeding when compared with STD. In a separate study, when the portal vein fructose concentration was selectively elevated to ~1 mmol/L under hyperglycemic and hyperinsulinemic conditions, hepatic concentrations of X5P were 49.2±4.2 nmol/g liver, whereas they were 10.2±1.2 nmol/g liver in the absence of fructose and 15±1.8 nmol/g liver when fructose was selectively increased in the portal vein to ~0.3 mmol/L [66]. Following meal ingestion or a 3-h elevation in the portal vein fructose concentration (~1 mmol/L), the liver was characterized by increased *G6Pase* gene expression, reduced serine phosphorylation of glycogen synthase kinase-3 (GSK3) and increased phosphorylation of cAMP response element binding protein (CREB) [61,66]. When the selective

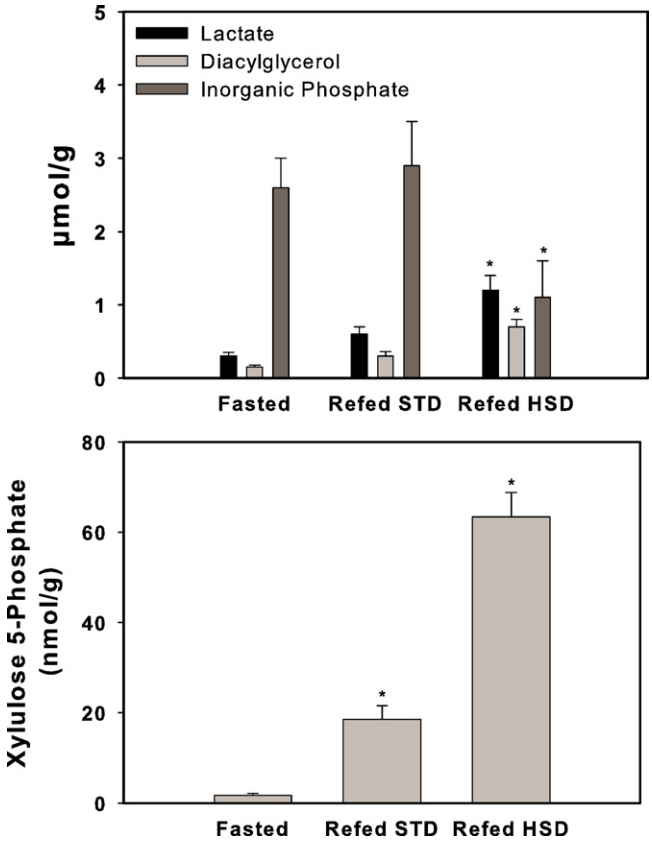

Fig. 1. Hepatic concentrations of lactate, diacylglycerol, Pi and X5P in fasted rats or in fasted rats that were refed a starch-enriched diet (STD) or a sucrose-enriched diet (HSD) for 3 h [61]. Values are means±S.E.M. (n=6–8). Fasted indicates 48-h fasted rats; refed STD indicates 48-h fasted rats that were refed a diet containing 68% of energy from corn starch, 12% from corn oil and 20% from casein; refed HSD indicates 48-h fasted rats that were refed a diet containing 68% of energy from sucrose, 12% from corn oil and 20% from casein. *P<.05, significantly different from the other two groups.

elevation in the portal vein fructose concentration was prolonged from 3 to 6 h, the liver was also characterized by increased c-jun N-terminal kinase (JNK) activity and phosphorylation of IRS-1 on serine 307 [12].

GSK3 is a serine/threonine kinase originally identified by virtue of its ability to phosphorylate and inactivate glycogen synthase [67]. Selective inhibition of GSK3 was shown to reduce the expression of both the *G6Pase* and phosphoenolpyruvate carboxykinase (*PEPCK*) genes in hepatoma cells [68]. The nuclear factor CREB interacts with the cAMP response element in genes controlled by the cAMP-mediated pathways of signal transduction. Included in this set of genes are *G6Pase* and *PEPCK* [69]. The cAMP-dependent protein kinase phosphorylates CREB at a single serine residue, Ser133, and creates a sequence motif that is a consensus site for GSK3 [69]. Hierarchical phosphorylation of CREB at these two sites appears to be necessary for the full activation of transcription by CREB [69]. To examine the contribution of reduced GSK3 phosphorylation in fructose-mediated induction of G6Pase, we employed a variation of the pancreatic-glucose clamp technique in combination with a commercially available inhibitor of GSK3 [66]. However, the use of this inhibitor had no effect on fructose induction of *G6Pase* gene expression. Thus, fructose induction of *G6Pase* gene expression appears to occur independently of GSK3. Whether fructose alters the transcriptional activity of CREB and the downstream consequences of CREB phosphorylation in response to increased fructose delivery has not been directly explored. The roles of JNK and serine phosphorylation of IRS-1 in fructose-mediated hepatic adaptations are discussed below.

2.1. Chronic exposure to diets enriched with sucrose or fructose induces hepatic insulin resistance

We have examined the impact of chronic changes in diet composition on hepatic glucose metabolism in rats to determine the ability of dietary nutrients to induce adaptations that characterize obesity and type 2 diabetes. In rats, diets enriched with sucrose increase hepatic gluconeogenesis and reduce the ability of insulin to suppress hepatic glucose production [14,51,60,70–72]. These diet-induced hepatic adaptations occur rapidly and independently of changes in body composition or circulating free fatty acids, leptin and corticosterone [14]. Similar adaptations occur in response to a fructose-enriched diet containing 34% of energy from fructose and 34% from glucose [15] and in response to a diet containing 18% of energy as sucrose [60]. Some or all of these adaptations have been observed by others [73–75].

To identify cellular targets responsible for the reduction in insulin suppression of hepatic glucose production, we anesthetized overnight-fasted male rats and injected them with either saline or insulin via the portal vein following the provision of either STD or HSD for 3 weeks [76]. Insulin stimulation of tyrosine phosphorylation of the insulin receptor was not different between groups; however,

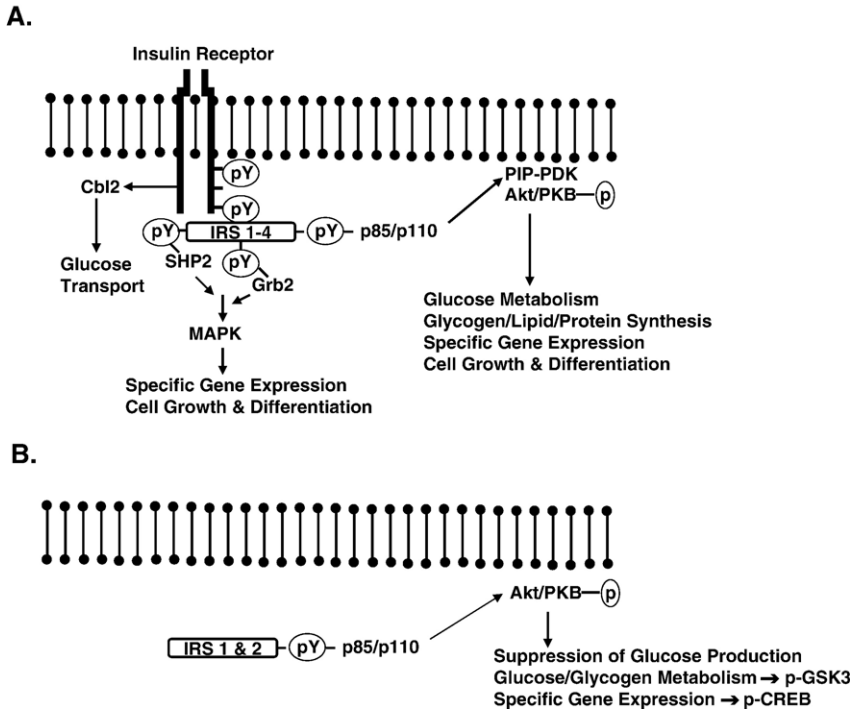

Fig. 2. Schematic representation of the general insulin-signaling pathway (A) and the sites in the insulin-signaling pathway of fructose-induced impairments (B). The presence of the plasma membrane in Panel B is provided as an anatomical reference.

tyrosine phosphorylation of IRS-1 and -2, association of IRS-1 and -2 with the p85 subunit of PI 3-kinase, PI 3-kinase activity and phosphorylation of Akt were significantly reduced in livers taken from HSD compared with STD. Thus, the HSD impaired postreceptor insulin signaling in the liver (Fig. 2). Similar impairments in hepatic insulin signaling have been observed in rats fed a high-fructose diet [77] and in response to the selective elevation of portal vein fructose concentrations to ~1 mmol/L under hyperglycemic and hyperinsulinemic conditions [66].

2.2. Mechanisms of sucrose- and fructose-induced hepatic insulin resistance

Insulin signaling can be attenuated by the actions of tyrosine phosphatase and serine/threonine kinase proteins, such as protein tyrosine phosphatase 1B (PTP1B) and JNK. PTP1B negatively regulates tyrosine phosphorylation of the insulin receptor and IRS proteins [78,79]. JNK also interferes with proximal steps in the insulin-signaling pathway, in part, through phosphorylation of serine 307 on IRS-1 [80,81]. Notably, JNK activity was abnormally elevated in muscle and adipose tissue of *ob*/*ob* and high-fat-diet-fed mice, whereas liver JNK activity was significantly increased in high-fat-diet-fed mice only [81]. When JNK −/− C57BL/6J mice were intercrossed with *ob*/*ob* C57BL/6J mice, adiposity was reduced and insulin action improved [81]. Thus, it has been proposed that JNK, in particular JNK1 in the liver, is a critical component of the biochemical pathway responsible for obesity-induced insulin resistance [81,82]. Genetic evidence has also demonstrated that increased JNK activity, caused by loss-of-function mutations in the JNK scaffold protein JNK-interacting protein-1 (JIP1), is causally linked to type 2 diabetes in humans [83].

Recent studies have observed increased expression of PTP1B protein in livers from fructose-fed hamsters [84] and elevated activator protein-1 activity (a downstream target of JNK) in livers taken from rats fed a high-fructose diet for 2 weeks [64]. We have examined the role of PTP1B and JNK in sucrose- and fructose-induced hepatic insulin resistance in some detail. Male rats were fed a control diet (STD, 68% of energy from corn starch, 12% corn oil, 20% casein) or a sucrose-enriched diet (HSD, 68% sucrose, 12% corn oil, 20% casein) for 1, 2 or 5 weeks [12]. HSD produced hepatic insulin resistance (based on tracer-estimated glucose production during a euglycemic, hyperinsulinemic clamp) at all time points. Hepatic PTP1B levels and activity were increased at 5 weeks only, whereas JNK activity was increased at all time points. Normalization of JNK activity in hepatocytes isolated from HSD rats improved insulin-stimulated tyrosine phosphorylation of IRS proteins and insulin suppression of glucose release. To examine the acute effects of HSD, we provided male rats STD for 1 week and then they were either fasted or fasted and refed STD or HSD for 3 or 6 h. Rats refed HSD were characterized by increased hepatic JNK activity and phosphorylation of IRS-1 on serine 307 after 6 h. To examine the effects of fructose specifically, we performed hyperglycemic and hyperinsulinemic pancreatic clamps for 3 or 6 h in the presence or absence of low (portal vein fructose concentration of <0.3 mmol/L) or high

(portal vein fructose concentration >1 mmol/L) intraportal fructose infusions. High intraportal fructose infusions increased hepatic JNK activity and phosphorylation of IRS-1 on serine 307 after 6 h. These data demonstrate that selective delivery of fructose can activate hepatic JNK activity and that this activation contributes to sucrose- and fructose-induced hepatic insulin resistance presumably through changes in serine phosphorylation of IRS-1.

2.3. Fructose and the activation of stress signaling in the liver

The mitogen-activated protein (MAP) kinase family of proteins are critical for the cellular response to a variety of extra- and intracellular stresses [85]. The MAP kinase JNK, in particular, is primarily activated by environmental stresses [85,86]. Distinct JNK family kinases have been implicated in multiple, specific biologic processes including insulin signaling [87,88]. MAP kinase pathways are assembled from a unique combination of protein kinases into distinct protein complexes or modules [86,88]. The minimal MAP kinase module contains a MAP kinase kinase kinase (MAP3K), a MAP kinase kinase (MAP2K) and a MAP kinase (MAPK; Fig. 3). The components of these modules interact via direct protein–protein interactions and/or are tethered to scaffold proteins [91–93]. This organized assembly affords several regulatory advantages, including protection against activation by irrelevant stimuli and spatial/temporal control [86,90]. Scaffold proteins such as JIP and JNK-associated leucine zipper protein (JLP) facilitate the assembly and regulation of JNK-signaling modules [91–93] (Fig. 3). In particular, JIP proteins (JIP1–3) may function to retain protein-signaling modules in the cytosol [93–95]. Although a considerable amount of work has been done to establish the role of JIP1 in regulating JNK and in the role of JNK in numerous biologic responses, less is known about how stress signals are linked to JNK activation and insulin action in the liver.

JNK is activated by sequential phosphorylation of a MAPK module, MAPK3→MAPK2→JNK (Fig. 3). There

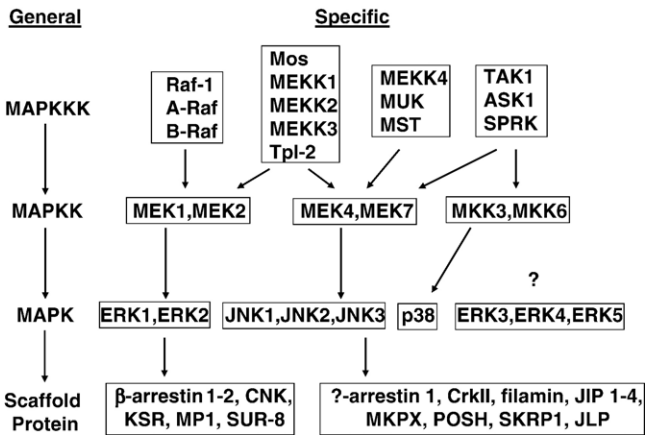

Fig. 3. Schematic representation of mammalian MAPK pathways. The figure was adapted from Boldt and Kolch [89] and Morrison and Davis [90].

are at least 12 MAP3Ks that have been identified, each of which can regulate multiple MAP2Ks and MAPKs [87,90]. In contrast, two MAP2Ks that regulate JNK, MKK4 and MKK7, have been identified [96]. Although both MKK4 and MKK7 appear to be required for full activation of JNK, differential phosphorylation of JNK by MKK4 or MKK7 may provide a molecular basis for selective regulation of JNK by various stimuli [87]. We have recently demonstrated that the signal generated by fructose delivery in the hepatocyte increases phosphorylation of MKK7 but not that of MKK4 [97]. Thus, it would appear that fructose delivery provokes the assembly of a MAPK-signaling module that includes MKK7 and JNK in hepatocytes. In our study, fructose was delivered to primary rat hepatocytes using a fructose-regenerating system, consisting of inulin and inulinase [97,98]. This system provides a more physiologic delivery of fructose and avoids large disturbances in hepatocyte ATP concentrations. Importantly, fructose delivery increased JNK activity and modulated the phosphorylation state of IRS proteins but did not lead to increased phosphorylation of nuclear targets of JNK, such as c-jun and ATF2. This selectivity of JNK action in response to fructose delivery may be mediated by the association of JNK with JIP1. Scaffold proteins such as JIP and JLP facilitate the assembly of JNK-signaling modules [90]. Another function of JIP proteins may be to sequester protein-signaling modules in the cytosol [91,93]. Thus, the selective activation of JNK and downstream targeting to IRS proteins in response to fructose delivery appears to involve a protein-signaling module that minimally includes MKK7, JNK and JIP1. Studies are underway to examine the direct role of these proteins in fructose-induced hepatic insulin resistance.

2.4. Cellular mediators of fructose-induced hepatic stress signaling

Activation of hepatic JNK in response to a single sucrose-enriched meal or selective fructose delivery in vivo and in vitro was selective (as it did not induce activation of p38 MAPK or ERK) but required a significant period of time (3–6 h), suggesting that the intrahepatic signal(s) involved may not include typical carbohydrate intermediates, such as phosphorylated sugars, X5P and lactate [12]. However, the potential contribution of these signaling metabolites cannot be excluded at the present time [99,100]. Moreover, fructose delivery in vivo or in vitro did not result in selective translocation of protein kinase C-α or -δ [12], suggesting that activation of JNK was not mediated via classical lipid intermediates [11]. Kelley et al. [64] reversed high-fructose-diet-induced hypertriglyceridemia and reduced activator protein-1 activation with lipooxygenase 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 [101]. Consistent with this notion, rats consuming a fructose-enriched diet (10% of energy) were characterized by elevated levels of aldehydes, particularly methylglyoxal [102]. Metformin, which has been used to lower elevated plasma methylglyoxal concentrations in type 2 diabetic subjects, was also able to prevent the development of sucrose-induced insulin resistance and cardiomyocyte dysfunction in rats [103,104]. Whether physiologic concentrations of these aldehydes mediate changes in hepatic stress signaling and/or cytotoxicity is currently unknown [101,105,106]. In addition, recent studies suggest that the relationship between aldehydes, stress signaling and cytotoxicity is highly complex [106,107]. Thus, additional studies are required to identify the cellular mediator(s) of fructose-induced hepatic insulin resistance and JNK activation and to determine whether aldehydes are causally linked to JNK activation in the hepatocyte.

3. 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 [7,108]. Sweet-corn-based syrups were developed during the past three decades and now represent close to one half of the calorie sweeteners consumed in the United States [7,109]. 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 [7,8,18]. However, direct experimental evidence demonstrating a causal relationship between added sucrose or fructose consumption and insulin resistance in humans is lacking.

In most cases, animal studies have used diets enriched with sucrose (32–69% of calories) or fructose (34–88% of calories) [74,75,77,110–112]. It should be noted, though, 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 [60]. In contrast, most "long-term" (>1 day) human studies typically have used amounts of sucrose ranging from 5% to 40% of total energy [113–121], although at least one study used a diet that contained 80% sucrose [117]. 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.

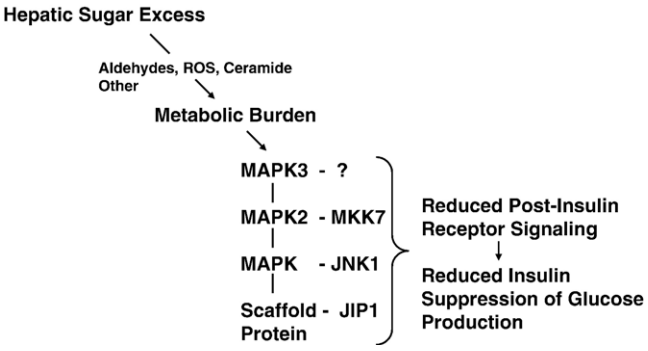

Fig. 4. Working model for sucrose- and fructose-induced insulin resistance in the liver.

The extent to which the hepatic adaptations to increased fructose delivery discussed in this review occur in humans will likely depend on the concentration of fructose presented to the liver, the duration of exposure to increased fructose delivery and multiple biologic and genetic factors [19]. However, it should be noted that very few human studies have employed appropriate methods to evaluate the effects of fructose on hepatic glucose metabolism or whole-body glucose production. In a recent study, seven normal men were provided a high-fructose diet (corresponding to an extra 25% of total calories) for 6 days [16]. The high-fructose diet not only increased fasting glycemia and triglycerides but also reduced the ability of insulin to suppress endogenous glucose production. Notably, the high-fructose diet had no effect on whole-body insulin-stimulated glucose disposal. These data are consistent with the notion that high rates of fructose delivery can impair insulin action in the human liver.

4. Working model

It is hypothesized that fructose, at high rates of delivery, leads to accumulation of intermediates that serve as acute, short-term signals of sugar excess (Fig. 4). Hepatic sugar excess inflicts a metabolic burden on the hepatocyte that selectively increases phosphorylation of MKK7, activation of JNK and association of JNK with IRS proteins and JIP1. Association of JNK with IRS-1 reduces tyrosine phosphorylation of IRS-1 and, thus, insulin signaling. Fructose delivery also reduces tyrosine phosphorylation of IRS-2 through mechanisms that are currently unknown. The intracellular signals that link fructose metabolism to hepatic stress signaling are currently unknown. Candidates include reactive aldehydes [64], reactive oxygen species [122] and novel lipid metabolites [123].

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