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REVIEW ARTICLE

Dietary fructose as a risk factor for non-alcoholic fatty liver disease (NAFLD)

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Abstract Glucose is a major energy source for the entire body, while fructose metabolism occurs mainly in the liver. Fructose consumption has increased over the last decade globally and is suspected to contribute to the increased incidence of non-alcoholic fatty liver disease (NAFLD). NAFLD is a manifestation of metabolic syndrome affecting about one-third of the population worldwide and has progressive pathological potential for liver cirrhosis and cancer through non-alcoholic steatohepatitis (NASH). Here we have reviewed the possible contribution of fructose to the pathophysiology of NAFLD. We critically summarize the current findings about several regulators, and their potential mechanisms, that have been studied in humans and animal models in response to fructose exposure. A novel hypothesis on fructose-dependent perturbation of liver regeneration and metabolism is advanced. Fructose intake could affect inflammatory and metabolic processes, liver function, gut microbiota, and portal endotoxin influx. The role of the brain in controlling fructose ingestion and the subsequent development of NAFLD is highlighted. Although the importance for fructose (over)consumption for NAFLD in humans is still debated and comprehensive intervention studies are invited, understanding of how fructose intake can favor these pathological processes is crucial for the development of appropriate noninvasive diagnostic and therapeutic approaches to detect and treat these metabolic effects. Still, lifestyle modification, to lessen the consumption of fructose-containing products, and physical exercise are major measures against NAFLD. Finally, promising drugs against fructose-induced insulin resistance and hepatic dysfunction that are emerging from studies in rodents are reviewed, but need further validation in human patients.

Keywords Insulin resistance · Inflammation · Metabolic syndrome (MetS) · Gut microbiota · Herbal medicine · Biomarkers · The brain · Ethanol · Humans · Oxidative stress · Liver regeneration · ATP

Abbreviations

CYP2E1	Cytochrome 450 2E1
ER	Endoplasmic reticulum
GLUT	Glucose transporter
HDL	High-density lipoprotein
HFCS	High-fructose corn syrup
HFD	High-fat diet
IR	Insulin resistance
IRS-1/2	Insulin receptor substrate 1/2
LCN2	Lipocalin 2
LDL	High-density lipoprotein
LPS	Lipopolysaccharide
Ltf	Lactoferrin
MC4R	Melanocortin receptor 4
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PAI-1	Plasminogen activator inhibitor-1
ROS	Reactive oxygen species
T2D	Type 2 diabetes mellitus
TG	Triglycerides

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TLR4 Toll-like receptor 4
TNF-α Tumor necrosis factor-α

Introduction

The liver is an essential organ for protein, fats, and carbohydrate metabolism as well as catabolism and excretion of toxins. Any functional impairment will therefore affect the whole organism and leads to significant morbidity and mortality. Non-alcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of pathological conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, and may ultimately lead to hepatocellular carcinoma (Conlon et al. 2013). The prevalence of NAFLD is estimated to be 20–30% of the general population in Europe and the USA (Gorden et al. 2011; Sapp et al. 2014). With an increase in the availability of high-calorie food, the use of fructose as a sweetener (e.g., in beverages) has been implicated in the increasing prevalence of the NAFLD and metabolic syndrome (MetS) (Bray et al. 2004; Vilà et al. 2011; Aroor et al. 2015). Fructose, a monosaccharide, naturally exists in fruits and vegetables. Fructose has the highest relative sweetness over other sugars; therefore, it is exploited in soft drinks and other commercial products (Montonen et al. 2007), particularly in the form of high-fructose corn syrup (HFCS). Dietary fructose is considered a risk factor for NAFLD and obesity (Bray et al. 2004; Nakagawa et al. 2006). However, the causal relationship between fructose consumption and liver pathogenesis still needs to be elucidated.

The understanding of the molecular, biochemical and pathological changes that cause the early-stages of NAFLD is a prerequisite to improve treatment strategies. This review is focused on the physiological influences of fructose consumption that lead to NAFLD and its associated abnormalities, such as the MetS, insulin resistance (IR), and disruption of gut microbiota. Furthermore, we suggest a novel hypothesis on how fructose may hit the liver and have reviewed possible therapeutic options against fructose-induced NAFLD. It also highlights how the brain regulates fructose intake and its adverse impact on the brain. This study recommends that more efforts should be taken to raise public awareness about the pros and cons associated with fructose consumption.

Fructose and glucose: global consumption and metabolism

Monosaccharide uptake and metabolism

Fructose is absorbed by enterocytes in the small intestine via GLUT2 and GLUT5 transporters (Soleimani 2011; Ritze et al. 2014) by both a partially active process and facilitated diffusion in rodents (Riby et al. 1993). D-Fructose inhibits its own transport, whereas the presence of glucose could facilitate transport of fructose in intestine and renal brush border membrane (Korieh and Crouzoulon 1991; Mate et al. 2001; Sloboda et al. 2014). Thereafter, fructose is delivered to the liver via the portal vein and taken up by GLUT2, GLUT5, and GLUT8 transporters on the surface of hepatocytes (Sakar et al. 2009; Soleimani 2011; Narasimhan et al. 2015). Hepatocytes of GLUT8-lacking mice failed to take up fructose and subsequently had an attenuated fructose-induced steatosis (DeBosch et al. 2014).

Although both glucose and fructose are metabolized through the glycolytic pathway, the rate-limiting enzyme (phosphofructokinase) is bypassed and the initial steps differ in fructose metabolism from that of glucose (Cha et al. 2008). When zebra fish were treated with 4% (w/v) fructose or glucose, only the fructose-treated larvae had developed NASH: abnormal mitochondrial and endoplasmic reticulum (ER), and activated inflammatory pathways (Sapp et al. 2014). Further differences between fructose and glucose metabolism were found at the molecular level. For instance, a reduction in the activity of the hepatic mitochondrial β-oxidation by fructose, but not glucose, was correlated with a decrease in the activity of peroxisome proliferator-activated receptor-α (PPARα), a nuclear receptor that plays a pivotal role in fatty catabolism (Rebollo et al. 2014), oxidative stress, and inflammatory response (Nan et al. 2014). Effects of fructose and glucose on cell cycle regulation in whole liver and skeletal muscle of rats have been reported using mini-array analysis (Fernández-Novell et al. 2014). Rats in this study received either 250 mg glucose/100 g body weight or 280 mg fructose/100 g body weight and the phosphorylation of several proteins was assessed. In the liver, glucose load induced a very intense increase in the serine phosphorylation levels of cyclin D3, total protein kinase C (PKC), ERK-2, protein phosphatase protein tyrosine phosphatase 1B (PTP1B), c-kit, and clathrin. The fructose load induced a significant increase in serine phosphorylation ERK-2, PTP2, cyclin D3, PI3 kinase/p85, and clusterin (Fernández-Novell et al. 2014).

Although many studies report differential activities of dietary fructose and glucose, some have found that fructose and glucose do have similar effects. Johnston and colleagues found no difference in liver triacylglycerol or biochemistry in healthy overweight men who ingested 25% fructose or 25% glucose energy diet for 2 weeks, followed by a 6-week "washout period", and resumed the diets again for 2-week interval (Johnston et al. 2013). Analogous effects of fructose and glucose on lipogenic gene expression and intermediary metabolism were found in human cell line (HepG2) in vitro (Hirahatake et al. 2011).

Global consumption of fructose and glucose

The use of fructose increased from 16% in 1978 to 42% in 1998 in the USA which coincided with an increase of the average daily intake (Vos et al. 2008; Marriott et al. 2009). It has been reported that the mean consumption of fructose has increased and was estimated to be 54.7 g/day and accounted for 10% of total Americans' daily caloric intake (Vos et al. 2008). Additionally, fructose contributes approximately 200–250 kcal/day (sucrose and HFCS are each half fructose), 7–8% of the current 2700 kcal/day *per* capita total calorie intake reported in the USA (White 2008). However, overall estimated carbohydrate intake also increased from 1978 to 2004. This means that the overall estimated mean total fructose intake when expressed as a percentage of carbohydrate intake declined in the same period (Marriott et al. 2009).

Recent reports also indicate that consumption of added sugars, including the HFCS, is decreasing in the USA (since 2005) (White 2008; Welsh et al. 2011). Nevertheless, the highest consumption of fructose (HFCS) is reported in the USA, Western countries (e.g., Canada, the Netherlands, Germany), South Korea, and Japan, while the lowest level of consumption is reported in India (White 2008; Marriott et al. 2009). In Italy, the mean daily intake of total, industrial, and fruit fructose in patients suffering from NAFLD was 18.0 ± 8.7 g, 6.0 ± 4.7 g, and 11.9 ± 7.2 g, respectively (Petta et al. 2013).

Fructose and NAFLD

Liver metabolism comprises a large variety of interrelated anabolic and catabolic functions which are performed complementarily in different anatomical zones (Gebhardt and Matz-Soja 2014). Simple steatosis is the accumulation of ectopic fat (deposition of triglycerides within cells of non-adipose tissue that normally contain only small amounts of fat) in the hepatocytes (Lettner and Roden 2008). Hepatic steatosis affects 20–30% of Americans and the population of the Western countries, who do not consume excessive alcohol (>30 g/day) (Bellentani et al. 2010). The most common cause of fatty liver can probably be attributed to increased caloric intake, which exceeds the rates of caloric expenditure (Birkenfeld and Shulman 2014). Simple steatosis has long been thought to be a relatively benign state of liver injury; however, clinical relevance indicates that 15–25% of patients could develop NASH. Importantly, up to 20% of patients have long-standing NASH and may develop fibrosis, cirrhosis, or even hepatocellular carcinoma over their lifetime (Ekstedt et al. 2006; Edmison and McCullough 2007; Fig. 1). The reason why a fatty liver progresses to develop inflammation and/or fibrosis, i.e., NASH, which is considered as the most violent form of NAFLD, is still unknown.

Fructose-induced NAFLD in humans

Important risk factors for the development of NAFLD in humans include low-physical activity, dietary factors, gut

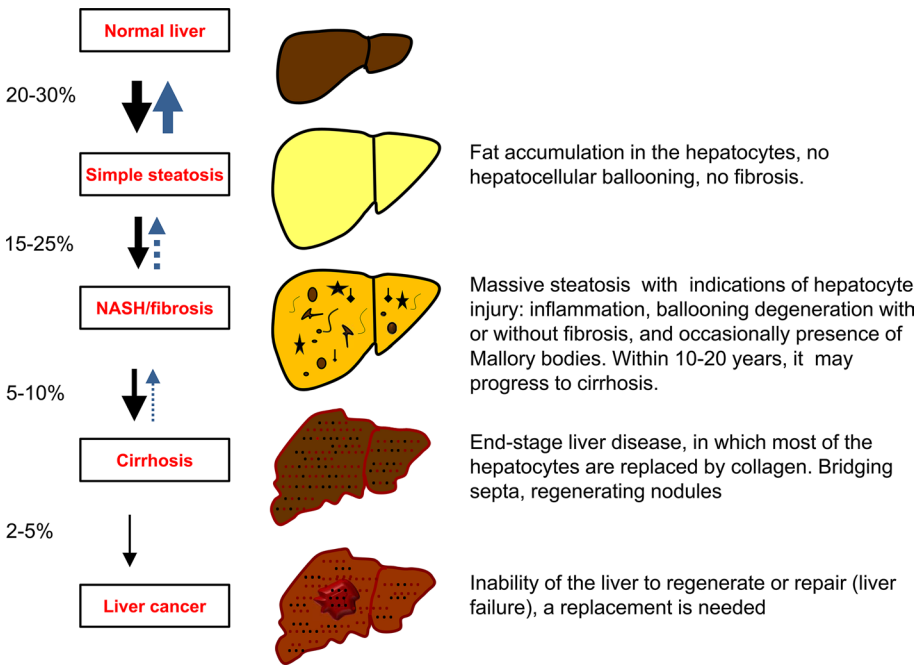

Fig. 1 Schematic of progression non-alcoholic fatty liver disease (NAFLD) depicts histological spectrum and estimated prevalence of the disease stages

microbiota, genetic and regulatory factors, and oxidative stress (Matz-Soja et al. 2016; Tilg et al. 2016). Here, we focus on aspects linked to dietary fructose. In general, high energy intake, inadequate energy compensation, and the special metabolism of fructose could explain the association between fructose and NAFLD (Assy et al. 2008; Ouyang et al. 2008; Rebollo et al. 2014).

One-year period of overeating of fruits rich in fructose, increased body weight, blood triglyceride, and transaminase levels in a 33-year-old male patient with insulinoma who was diagnosed NAFLD (Rokutan et al. 2015). Increased fructose intake is also associated with decreased hepatic insulin sensitivity and increased fibrosis severity in patients with NASH (Yki-Järvinen 2010). Similar effects have been seen in human studies where short-term (9d consecutively) fructose intake (25% of energy content) was associated with increased hepatic fatty acid synthesis and liver fat in healthy men fed weight-maintaining diets (Schwarz et al. 2015). In NAFLD patients, increased daily fructose ingestion was strongly associated with low high-density lipoprotein (HDL) cholesterol, increased caloric intake, hyperuricemia, increased fibrosis severity, and increased hepatic inflammation and hepatocyte ballooning (Abdelmalek et al. 2010). Overweight subjects who received fructose-sweetened beverages for 10 weeks had a significant increase in visceral adipose tissue, dyslipidemia, and an impaired glucose tolerance compared to the corresponding glucose cohorts, although weight gain was not different in either cohorts (Stanhope et al. 2009; Tappy et al. 2013). Other work has found that consumption of honey, sucrose, and HFCS (55%) produces similar metabolic effects in glucose-tolerant/glucose-intolerant individuals who consumed 50 g carbohydrate daily from assigned sweeteners (Raatz et al. 2015; Basaranoglu et al. 2015). Despite similar overall energy, the total fructose intake was found to be significantly higher in NAFLD patients compared to healthy individuals (Thuy et al. 2008) further highlighting the significant consequences of fructose consumption in NAFLD. In support of such findings a pilot intervention study focusing on the reduction of fructose intake over 6 months provided some evidence for a significant impact on reduction of intrahepatic fat content of NAFLD patients (Volynets et al. 2013).

Concerning the comparison of fructose and glucose effects the observation that plasma adropin concentrations vary in response to dietary sugar intake in human subjects, irrespective of duration, sex or age, is intriguing. Adropin is a peptide hormone encoded by the *Energy Homeostasis Associated* (*ENHO*) gene that regulates whether the body burns fat or sugar during feeding and fasting cycles (Butler et al. 2015). Glucose consumption reduced plasma adropin levels, whereas fructose consumption increased plasma adropin levels. However, the consumption of HFCS as 25% of daily energy requirements had no effect through 10 weeks of the study (Butler et al. 2015). Overall, these studies indicate that both the quality and quantity of ingested carbohydrate are important risk factors for NAFLD and its correlated abnormalities.

Although these findings support the pathological role of fructose, data from human studies about the long-term effects of fructose intake are criticized to have limitations concerning their sample size and retrospective nature (Sloboda et al. 2014) and a recent meta-analysis of six observational and 21 intervention studies carried out by Chung and co-workers concluded that the apparent association between indexes of human health (i.e., liver fat, hepatic de novo lipogenesis and others) and fructose or sucrose intake appear to be confounded by excessive energy intake (Chung et al. 2014). Other meta-analysis studies cited in (Bray and Popkin 2014), however, gave opposite conclusions. Thus, even at the level of meta-analyses, there is no general agreement and large and comprehensive interventions studies are urgently needed to clarify the exact role of fructose in NAFLD and MetS in human subjects.

Animal studies

Animal studies provided additional evidence on the role of fructose-/HFCS-induced hepatic steatosis. In rodents, consumption of fructose has been associated with increased periportal fibrosis, dyslipidemia, ER stress, and impaired insulin signaling (Kawasaki et al. 2009; Ren et al. 2012). Typical features of human NASH including excessive steatosis, hepatocellular ballooning, inflammation, and fibrosis were reproduced by the addition of fructose to saturated fat (Fig. 2) and cholesterol diets in animals (Charlton et al. 2011). Maternal fructose intake resulted in age- and sex-specific changes in fetal, placental, and neonatal free fatty acid metabolism, which may be associated with disruptions in core clock gene machinery in rats (Clayton et al. 2015). Results from many other experimental studies are presented further down in their specific context.

Pathogenic mechanisms

An imbalance in fatty acid synthesis, β-oxidation, and TG exportation processes leads to the accumulation of fat in hepatocytes. High-caloric diets could also contribute in this process. As mentioned, fructose is efficiently converted into glyceraldehyde-3-phosphate by avoiding the rate-controlling step of glucose metabolism in hepatocytes. Thus, the consumption of fructose-enriched diets increased

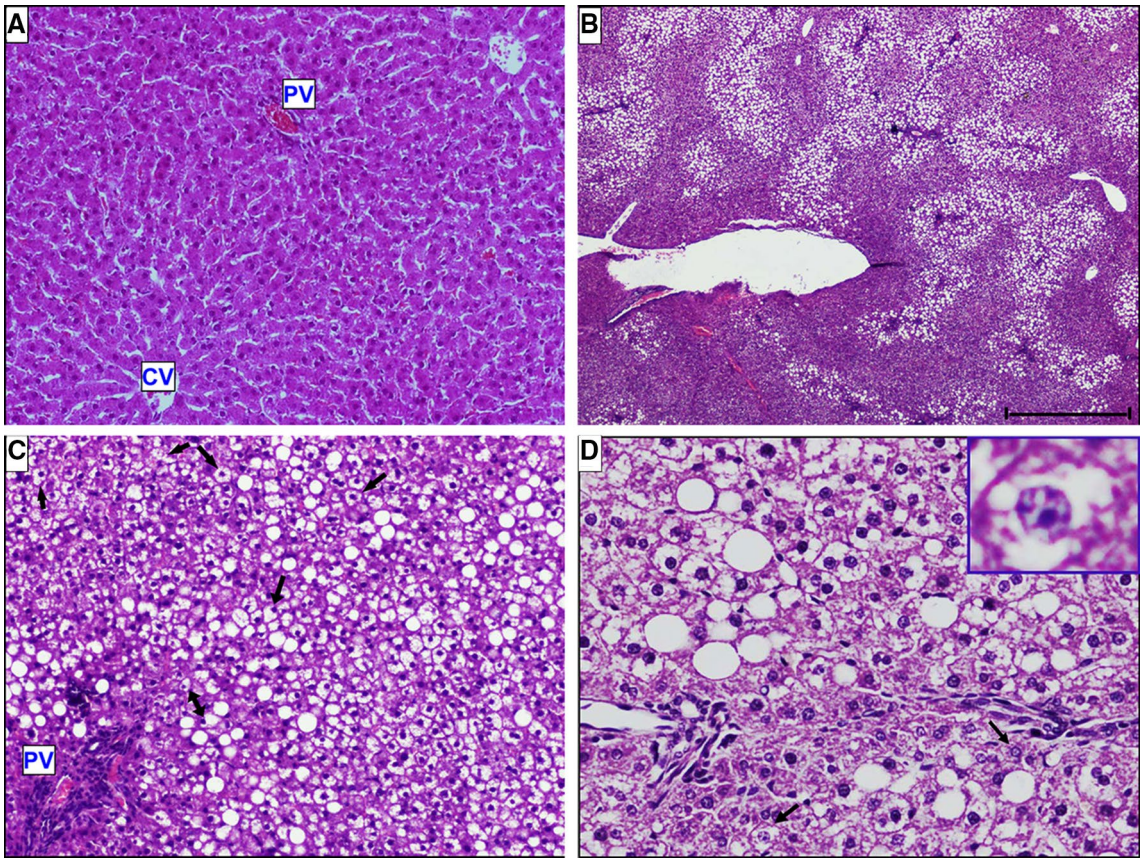

Fig. 2 Representative photomicrographs of HE stained liver sections. **a** "Normal" rat liver structure, **b** an overview microsection of the high-fructose-induced NAFLD (×20), **c** macrosteatotic hepatocytes and portal inflammation in Zone I, while hepatocytes ballooning with central nuclei in the centrilobular area (×100), **d** nuclear vacuolation of hepatocytes *inset* ×200 and *arrows*. Many hepatocytes show nuclear vacuolation, a feature much more commonly seen when fatty liver has a non-alcoholic etiology. Hepatic simple steatosis in which >5% of the parenchyma histologically manifest intracytoplasmic TG

de novo lipogenesis and the activities of hepatic lipogenic enzymes fatty acid synthase and stearoyl-CoA-desaturase-1 (Crescenzo et al. 2013). These conditions sensitize the liver to inflammation; a key pathophysiologic feature of NASH (Renaud et al. 2014), and increase mitochondrial coupling leading to oxidative stress (Crescenzo et al. 2013). Another important point in this regard is that high-fat and high-sugar (Western) diet-induced steatohepatitis that was dependent on fructokinase, suggesting a key role for fructose (derived from sucrose) in this development of NASH (Ishimoto et al. 2013). It is, however, not only dietary fructose which causes a metabolic imbalance, but also the endogenous fructose production and metabolism in the liver that was found to contribute to the development of the MetS (Lanaspa et al. 2013). Song et al. stated a novel mechanism for obesity-related fatty liver, in which fructose absorption from the duodenum impaired copper absorption and increased *de novo* lipogenesis (Song et al. 2012).

Fructose-dependent derangement of liver regeneration and ATP depletion

It has been intensively studied that fructose uptake exerts an acute ATP depletion by flooding the hepatocytes with fructose-1-phosphate via fructokinase (Boesch et al. 1997; Latta et al. 2007; Kanuri et al. 2011a). Patients with overt type 2 diabetes mellitus (T2D) can exhibit reduction in hepatic ATP synthesis and impaired repletion of their hepatic ATP stores upon ATP depletion by fructose (Koliaki 2013). Consequently, hepatocytes are prevented from proliferation as well as from entering apoptosis (Speicher et al. 2012). Instead, they may switch to a special senescent phenotype exhibiting abnormal metabolic features (e.g., increased production of urate, steatotic rewiring) and other aberrant cellular functions. Altogether, these changes impair normal liver regeneration and favor the activation of precursor cell-driven regenerative pathways. Since senescent hepatocytes may have a higher risk of dying

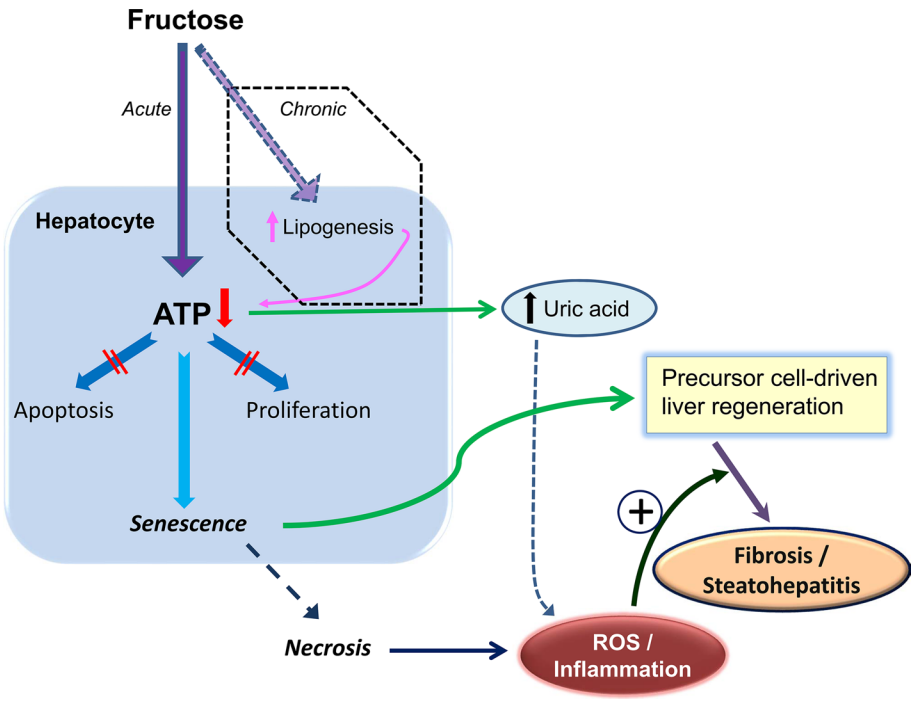

Fig. 3 Hypothesis on fructose-dependent derangement of liver regeneration. Acute fructose uptake results in a dramatic drop of hepatocellular ATP levels. This may enhance hepatocytes to become senescent. Altogether these changes impair normal liver regeneration and favor the activation of precursor cell-driven regenerative pathways. ATP depletion results in uric acid over-production, which in turn promotes the formation of reactive oxygen species (ROS) and inflammation. Senescent hepatocytes are more likely to undergo necrotic pathway. Inflammatory reactions and fibrogenesis can be also induced

via necrosis (Rashid et al. 1999), inflammatory reactions may be induced which impact on hepatic precursor cells at all regenerative stages and support fibrotic degeneration as well as progression to steatohepatitis (Fig. 3). Under chronic fructose intake, on the other hand, the main effect, on the hepatocytes, seems to be an insufficient replenishment of ATP (Cortez-Pinto et al. 1999; Abdelmalek et al. 2012). This effect is definitively associated with steatosis, but it is not fully explained yet at molecular levels. Transient depletion of cellular ATP levels were found in cultured primary human hepatocytes (Weiland et al. 2012), but not in human liver cancer cell lines such as HepG2, HuH7, Hep3B, and PLC/PRF/5 (Weiland et al. 2012).

Fructose intake increases the production of uric acid

Using MR imaging and the association between body mass index (BMI) and ATP homeostasis was assessed in healthy subjects with a broad range of BMIs and without any known liver disease (age 18–60 years, and daily alcohol drink ≤20 g) (Nair et al. 2003). Reduced hepatic ATP stores were shown to be more prevalent in overweight and obese subjects than in lean subjects (Nair et al. 2003). This can be assessed by the rate of production of uric acid by hepatocytes as it is degraded as a sensitive index of compromised cell ATP homeostasis (Petrie et al. 2013). Fructose differs from other sugars also in its ability to cause intracellular hepatic ATP depletion, nucleotide turnover, and the generation of AMP and uric acid (Lanaspa et al. 2012a; Johnson et al. 2013). Higher dietary fructose was found to associate with impaired hepatic ATP homeostasis in obese individuals with T2D (Abdelmalek et al. 2012). In this regard, subjects with high uric acid show a greater level of impaired hepatocellular energy homeostasis in response to fructose suggesting that fructose is a risk factor for progressive liver injury (Abdelmalek et al. 2012). In keeping with this, recent studies have shown that consumption of 25% of energy requirements of fructose-sweetened beverages for 10 weeks increases circulating concentrations of uric acid and retinol-binding protein-4 (RBP-4) in overweight/obese humans (Cox et al. 2012). This could lead to further fat deposition as fructose-induced uric acid generation causes mitochondrial oxidative stress that stimulates fat accumulation independent of excessive caloric intake, and may have a causal role in diabetes and obesity (Lanaspa et al. 2012b; Speicher et al. 2012; Johnson et al. 2013). These studies suggest that raised plasma uric acid could be a marker of compromised hepatic ATP homeostasis.

Fructose intake and oxidative stress

Pathological oxidative stress arises due to an imbalance of reactive oxygen species (ROS) and antioxidant production, altering the normal redox state of cells (Barker et al. 2014). ROS sources within the cells include the mitochondria, peroxisomes, NADPH oxidase in the plasma membrane of activated macrophages, and others (Fig. 4). Factors promoting lipid peroxidation and oxidative stress include the induction of CYP2E1 and mitochondrial dysfunction favoring the formation of ROS (Pessayre and Fromenty 2005),

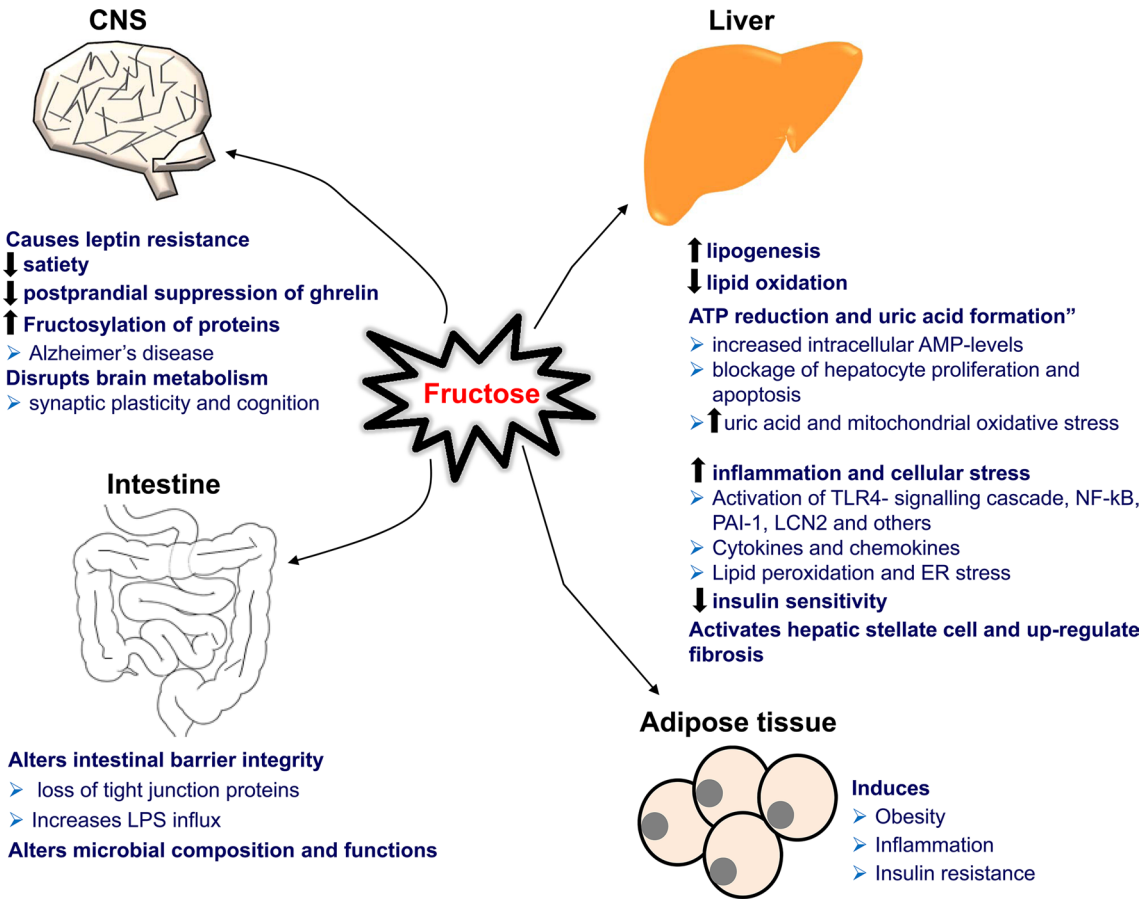

Fig. 4 Potential main deleterious effects of fructose intake

increased lipid oxidation by-products and the cytokines. Both oxidative stress and ER stress, which are important factors in the progression of simple steatosis to NASH, were able to independently cause hepatic lipid accumulation. Treatment of larvae of zebra fish with fructose-containing culture medium which also includes valinomycin (an oxidative stress-inducing agent), or tunicamycin, (an ER stress-inducing agent) resulted in the accumulation of lipid in the liver. The fructose-treated fish exhibited similar expression profiles of lipogenic and inflammatory genes seen in the valinomycin-treated group (Sapp et al. 2014). Fructose also induces an imbalance in gut microbiota and bacterial by-products that can promote the onset of NAFLD and its correlated abnormalities (see below). Exendin-4 (GLP-1 analogs) reduces human primary hepatocyte steatosis and improves survival by enhancing the unfolded protein response and promoting macroautophagy by decreasing the oxidative stress (Sharma et al. 2011). Lim et al. describes that NAFLD is characterized by two steps of liver injury (the 'two-hit' theory). In the first 'hit,' hepatic metabolism of fructose promotes intrahepatic lipid accumulation (steatosis), inhibition of mitochondrial β-oxidation of long-chain fatty acids, hepatic and skeletal muscle insulin resistance, and hyperglycemia. In the second 'hit,' owing to the molecular instability of its five-membered furanose ring, fructose promotes protein fructosylation and formation of ROS, which require quenching by hepatic antioxidants (Lim et al. 2010).

Insulin resistance

IR is known to be an underlying cause of T2D, cardiovascular disease, and the MetS (Kelishadi et al. 2014). Physiologically, IR is a condition where higher than normal insulin levels are needed to adequately transport glucose due to the decreased response of peripheral tissues, and to suppress the hepatic glucose production. As the liver is a major depot for glucose uptake and storage, hepatic IR leads to further elevation in blood glucose levels (Michael et al. 2000). Fructose ingestion reduces insulin sensitivity. In young rats given fructose-enriched drinks for 12 weeks, there was a significant increase in fasting glycemia, systolic blood pressure, and presented IR (higher HOMA-IR) compared to controls (Dupas et al. 2016).

Hepatic IR is also a major contributor to steatosis in the pathogenesis of NAFLD, which could be attributed to impaired insulin-stimulated IRS-1/2 tyrosine phosphorylation, and the expression of the microsomal CYP2E1 is important in this context (Samuel et al. 2004). As a consequence of excessive fructose-triggered lipid accumulation in the hepatocytes; harmful conditions such as mitochondrial dysfunction, ER stress, inflammation, and hepatic IR could be occurred (Birkenfeld and Shulman 2014; Pyo and Lee 2014).

Fructose and gut microbiome and inflammation

Emerging evidences demonstrate that intestinal microbiome is among the key components in the progression of NAFLD. Due to its anatomical links to the gut, the liver is constantly exposed to gut-derived endotoxins delivered via portal vein and thus functions as the bodies first line of defense (Mouzaki et al. 2013). Kupffer cells are the resident macrophages in the sinusoids and are able to process bacteria and endotoxins, thereby playing a major role in the protection against septicemia. More than 90% of bacterial phylogenetic types encompassing the mouse distal gut microbiota belong to the Bacteroidetes and Firmicutes phyla, similar to that in human beings (Frank et al. 2007). Aron-Wisnewsky et al. reported that intestinal-bacterial patterns appear to vary between obese and lean humans (Aron-Wisnewsky et al. 2013), and patients with NAFLD have more frequently bacterial overgrowth than controls (Wigg et al. 2001).

Mechanism of fructose-induced bacterial translocation and the onset of NAFLD

The consumption of fructose may contribute to the onset of NAFLD through mechanisms involving an increased translocation of intestinal-microbial components, altered concentration of TLR, and activation of TLR-dependent signaling pathways (Spruss et al. 2009). Indeed, feeding monkeys with fructose for 6 weeks caused a rapid liver damage secondarily to microbial translocation and increased incidence of T2D (Kavanagh et al. 2013). In fructose-fed *Tlr4*$^{-/-}$ mice; hepatic steatosis, lipid peroxidation, and TNFα levels were significantly reduced compared to fructose-fed wild-type mice (Spruss et al. 2009). A long-term intake of fructose was associated with a marked reduction in the protein concentration of the tight junction protein in the duodenum (Spruss et al. 2012b). Mice fed HFD and fructose together showed a higher infiltration of lymphocytes into the liver and a lower inflammatory profile of Kupffer cells than mice fed HFD alone. The dysbiosis (a microbial imbalance) associated with dieting showed that fructose specifically prevented the decrease in intestinal bacteria in HFD-fed mice and increased *Erysipelotrichi* in mice fed with fructose, independently of the amount of fat. These data highlight that the complexity of diet composition could impact the development of liver lesions during obesity (Dupas et al. 2016). The number of members of two bacterial genera, *Coprococcus* and *Ruminococcus*, were increased by the fructose-rich diet and reduced by both antibiotic and fecal treatments in rats, pointing to a correlation between their abundance and the development of the MetS (Di Luccia et al. 2015). These studies therefore indicate the importance of gut microbiota in fructose-induced NAFLD and T2D.

Postprandial acute effects of fructose consumption were investigated as well. The sucrose- or fructose-fed mice had a low-grade inflammatory response which includes leukocytosis and high serum concentrations of pentraxin-3, leptin, and resistin. An intensified inflammatory response concomitant with an increased liver influx of neutrophils and dropping of the adiponectin concentration was found in mice following a fructose-containing meal (Rodrigues et al. 2014).

Fructose and the brain

The hypothalamus is a major area in the brain where nutritionally relevant information originating from the peripheral organs is integrated (Li et al. 2015).

Fructose effects and potential mechanisms

Fructose feeding up-regulates rat brain GLUT5, suggesting fructose entry. It was reported that fructose-conditioned preferences in rats were based primarily on the sugar's palatable taste, while glucose preferences were based on its taste as well as its postingestive actions. Dopamine antagonists differentially blocked fructose-conditioned preferences acquisition and expression in different regions of the brain (Sclafani and Ackroff 1994; Malkusz et al. 2015).

Endocannabinoids have been implicated in the regulation of the consumption of palatable food. It was found that fructose drinking affects enzymes involved in the metabolism of hypothalamic endocannabinoids and this predates obesity in rats (Erlanson-Albertsson and Lindqvist 2010). The short-term effect of sucrose, glucose, or fructose solutions on peripheral and central appetite signals in rats was also studied. Consuming sugar solutions resulted in increased serum leptin, decreased peptide-YY, and down-regulated hypothalamic *Neuropeptide-Y* mRNA. Fructose drinking increased serum ghrelin. Moreover, consumption of sucrose or fructose solution resulted in up-regulated hypothalamic cannabinoids mRNA (Lindqvist et al. 2008).

Melanocortin receptor-4 (MC4R), a receptor for the α-MSH and leptin in the brain and liver, plays a key role in the regulation of lipid metabolism (Xu et al. 2013). *Mc4r* deficiency increases appetite and diminishes satiety and is the most common cause of monogenic obesity (Albuquerque et al. 2014). In addition, sex differences in brain *Mc4r* expression was found in mice (Qu et al. 2014). Maternal and post-weaning high-fat diet predisposes the offspring for obesity, glucose intolerance, and IR in later life. The hypothalamus expression of *Mc4r* was significantly increased in mouse offspring fed a high-fat, high-sucrose diet during gestation into 32 weeks (Zheng et al. 2015). High-fructose intake during pregnancy modulated the hepatic and hypothalamic AMPK signaling pathways in female offspring after birth (Mukai et al. 2014). Maternal high-fructose diet has also long-term effects on brain mitochondrial function in aging rats, which appears to be linked to an increase in levels of mitochondrial uncoupling protein-5 (Mortensen et al. 2014). Moreover, high-fructose consumption exacerbated the pathology of brain trauma by further disrupting energy metabolism and brain plasticity (Agrawal et al. 2015).

Monosaccharides activate distinct neuronal circuits to promote feeding behavior (Rorabaugh et al. 2014). Compared to glucose, fructose-given Drosophila flies were obese, consumed more food, and the brain mRNA expression of insulin-related peptides was reduced (Rovenko et al. 2015). Overnight fasted, normal-weight healthy volunteers without diabetes and with a mean age of 31 years have been given 75 g fructose or glucose during MRI scanning. Consumption of fructose resulted in a distinct pattern of hypothalamic regional cerebral blood flow (CBF) and a smaller increase in systemic glucose, insulin, and glucagon-like polypeptide 1 levels compared with subjects fed an isocaloric amount of glucose (Page et al. 2013). The increased food intake was attributed to the rapid initial steps of fructose metabolism in the brain, provoking an immediate drop in the ATP/AMP ratio, increased AMPK activity, decreased acetyl-CoA-carboxylase activity, and malonyl–CoA amount in the hypothalamus (Cha et al. 2008).

Substances that could counteract fructose-induced brain deterioration

Lycopene, a member of the carotenoid family of phytochemicals, exhibited protective effects against brain damage resulting from fructose-caused IR, neuro-inflammation, and reduced activity of cholinergic system in rats (Yin et al. 2014). Nutrient betaine (a metabolite of choline and a component of methionine–homocysteine cycle) has protective effects against diet-induced NASH and neural injury. Interestingly, betaine inhibited fructose-caused hypothalamic astrocytosis by inhibiting TLR4/NF-κB pathway and histone deacetylases-3 overexpression in rats (Li et al. 2015). Analogously, increasing angiotensin-(1–7) levels in the brain were found to attenuate cardiovascular and metabolic disorders in fructose-fed rats (Guimaraes et al. 2014). Moreover, curcumin (an effective scavenger of ROS and nitrogen species) protected against neuronal damage in hippocampal dentate gyrus of fructose-fed mice by inhibiting microglia activation and suppressed fractalkine/CX3C-Recptor1 up-regulation in the neuronal network (Xu et al. 2016).

Fructose and alcohol

The hepatocytes play important functions in detoxification of poisons, e.g., alcohol (Pastoret et al. 2013). As introduced, NAFLD encounters none or mild-to-moderate alcohol consumption. The cutoff value for a tolerable alcohol consumption in NAFLD suspected patients ranges from absence, >1 drink/day (10 g alcohol) to 30 g/day (Dam-Larsen et al. 2004).

Similarities in metabolism and post-ingestion consequences

Lustig (Lustig 2010) has reported that there are similarities in fructose and ethanol metabolism in the liver in these aspects:

- Both serve as substrates for *de novo* lipogenesis and promote hepatic IR, dyslipidemia, and hepatic steatosis
- Fructosylation of proteins with resultant superoxide formation similar to acetaldehyde, an intermediary metabolite of ethanol
- Promoting sensations of hunger via blocking of leptin signaling.

Nevertheless, a few studies have described the consequences of combined consumption of fructose and ethanol on liver pathology or their potential synergistic effects.

Acute concurrent consumption

The acute effect of fructose administered intravenously or orally with an alcoholic drink on liver metabolism or alcohol clearance from bloodstream has been investigated clinically (Boesch et al. 1997; Onyesom 2005). Fructose had beneficial effects against alcoholic intoxication, whereby it caused a significant increase in the rate of decrease of blood ethanol levels (Brown et al. 1972; Uzuegbu and Onyesom 2009). It has been reported that honey (naturally contains fructose) reduced blood alcohol concentration but did not affect the level of serum malondialdehyde (MDA, a marker for lipid peroxidation) and glutathione peroxidase

activity in intoxicated male mice (Shi et al. 2015). In mice, pharmacological activation of aldehyde dehydrogenase-2 by Alda-1 reversed liver damage through accelerating aldehyde clearance, and upregulated fatty acid catabolic enzymes and thus reversed steatosis (Zhong et al. 2015). Interestingly, it was suggested that fructose stimulates ethanol oxidation, increasing the rate of oxidative phosphorylation. Consequently, the capacity of the respiratory chain for oxidizing reducing equivalents derived from ethanol is enhanced (Scholz and Nohl 1976). The change in alcohol metabolism in the presence of fructose has been linked to the ratio of NAD^+/NADH, which facilitates alcohol oxidation by a complementary mechanism (Alwahsh et al. 2014a).

Chronic ethanol and fructose consumption

Long-term ingestion of fructose and ethanol together exaggerated liver dysfunction (Song et al. 2016), dyslipidemia, and IR compared to each diet separately (Alwahsh et al. 2014a). In NAFLD patients, fasting blood ethanol was found to be at a high level, which is suggested to be due to an increased endogenous ethanol synthesis in the gastrointestinal tract. This increase in blood ethanol levels in NAFLD patients may result from insulin-dependent impairments of alcohol dehydrogenase (ADH) activity in liver tissue rather than from an increased endogenous ethanol synthesis (Engstler et al. 2015). Studies on mouse primary hepatocytes have shown individual exposure to ethanol or fructose did not sensitize the hepatocytes to TNFα-induced necroptosis. However, concurrent exposure of hepatocytes to fructose and ethanol synergistically promoted mitochondrial sensitivity to TNFα (Shulga and Pastorino 2014). It has also been demonstrated that CYP2E1 plays an important role in ethanol metabolism, and CYP2E1 inhibition by chlormethiazole blunted ethanol-induced lipid peroxidation, oxidative stress, and the inflammatory response in human hepatoma cell line expressing CYP2E1 (Mahli et al. 2015). Interestingly, dioscin, a natural steroid saponin, widely exists in many herbs and has demonstrated protective effects against ethanol-induced liver injury (Xu et al. 2014). Plasma ceruloplasmin activity and plasma copper levels were shown to be significantly lower in the mice fed with either high-fructose-diet or alcohol (Song et al. 2016). In contrast, liver copper levels as well as plasma copper levels were significantly higher in mice fed an alcohol-plus-high-fructose-containing diet compared to mice fed chronic alcohol alone (Song et al. 2016). Studying fructose and ethanol metabolism will increase our understanding of NAFLD and ALD pathogenesis and their clinical overlap.

Mediators that are altered in fructose-onset NAFLD

Here we underscored selective markers of which their protein expression and levels are changed in plasma and/or in liver (Table 1).

Lipocalin-2 (*LCN2*) is a 25-kDa secretory glycoprotein originally detected in neutrophil granulocytes and tissues that are exposed to microorganisms (Ahmad et al. 2014). LCN2 plays roles in the acute-phase response, apoptosis, and tissue homeostasis (Borkham-Kamphorst et al. 2011). LCN2 has been also described as a critical regulator of energy metabolism (Guo et al. 2010). Additionally, LCN2 has been proposed as a biomarker to discriminate between sample steatosis and fructose-induced NASH in rats (Alwahsh et al. 2014b).

Plasminogen activator inhibitor-1 (*PAI-1*) is also an acute-phase protein, the expression of which was increased in the liver and plasma, and correlated with endotoxin concentrations and total carbohydrates intakes in NAFLD patient compared to controls (Thuy et al. 2008). Experimentally, it has been shown that *Pai-1*$^{-/-}$ mice are protected from weight gain and marked hepatic lipid accumulation in a model of high-fat/high-carbohydrate feeding (Kanuri et al. 2011b). PAI-1 has a causal role in mediating the early phase of fructose-induced liver damage through signaling cascades downstream of Kupffer cells and tumor

Table 1 Biomarkers known to change during fructose-induced fatty liver disease

Parameter	Presence	
ALT	Serum	Kanuri et al. (2011b)
Leptin	Serum	Alwahsh et al. (2014b)
Insulin	Serum	Alwahsh et al. (2014a)
RBP-4	Serum	Cox et al. (2012)
Uric acid	Serum and liver	Abdelmalek et al. (2012), Johnson et al. (2013)
Adiponectin	Serum	Spruss et al. (2012a)
MDA	Serum	Volynets et al. (2010)
Homocysteine	Serum	Li et al. (2013)
PAI-1	Serum and liver	Kanuri et al. (2011b)
LCN2	Serum and liver	Alwahsh et al. (2014b)
TNF-α	Serum and liver	Kanuri et al. (2011a)
4-HNE	Liver	Volynets et al. (2010)
TLR4	Liver	Spruss et al. (2009)
iNOS	Liver	Spruss et al. (2011)
Sirt1	Liver	Feige et al. (2008)

RBP-4 retinol-binding protein-4, *MDA* malondialdehyde, *4-HNE* 4-hydroxynonenal, *iNOS* nitric oxide synthase

necrosis factor-α (TNF-α) (Kanuri et al. 2011b). Similar to *nitric oxide synthase* (*iNOS*), PAI-1 may be a critical factor in mediating the effect of the increased translocation of bacterial endotoxin and the subsequent activation of toll-like receptor (TLR)-4-dependent signaling cascades found in livers of mice chronically exposed to fructose (Kanuri et al. 2011b). The sex-specific differences in the susceptibility to the development of NAFLD were associated with the regulation of the adiponectin-AMPK-PAI-1 signaling, in which the expression of hepatic PAI-1 was markedly induced in female mice (Spruss et al. 2012a).

In a related context, fructose-induced hepatic steatosis and increased translocation of endotoxins were associated with an increased formation of ROS in the liver and expression of hepatic *TNF-α*, a pro-inflammatory cytokine, secreted mainly by activated macrophages (Bergheim et al. 2008). TNF-α both promotes and is activated by IR, and it also antagonizes adiponectin, an anti-inflammatory adipocytokine (Tiniakos et al. 2010). Furthermore, TNF-α receptor $1^{-/-}$ (*Tnfr1*$^{-/-}$) mice were protected from the onset of fructose-induced steatosis and IR (Kanuri et al. 2011a), highlighting the essential role of TNF-α in triggering of NAFLD (Tomita et al. 2006; Martius et al. 2014). Conversely, it was reported that fructose protected murine hepatocytes from TNF-induced mitochondrial apoptosis by modulating JNK signaling, thereby blocking bid-mediated activation in a protein kinase A-dependent manner (Speicher et al. 2012).

Leptin (Ob) is a 16-kDa protein primarily secreted by adipocytes. Leptin affects the immune system and plays a remarkable role in the regulation of lipid and glucose metabolism in the liver (Lou et al. 2010) through the leptin receptor (Ob-R) (Lou et al. 2010). High-fructose-enriched diet had significantly elevated serum leptin levels in fasted rats (Alwahsh et al. 2014a, b). An orally given leptin potentiated a fructose-induced (1) increase in blood glucose and mRNA levels of key gluconeogenesis enzymes, and (2) an increase in blood triglycerides and hepatic lipogenic gene expression. Dietary fructose triggers the release of gastric leptin which, in turn, up-regulates GLUT5 and concurrently modulates metabolic functions in the liver. This could explain, in part, the rapid lipogenic and deleterious effects of fructose (Sakar et al. 2009).

Increased serum *uric acid* levels serve as a biomarker for increased fructose consumption (Abdelmalek et al. 2012). One additional mediator is *sirtuin-1* (*Sirt1*), a NAD^+-dependent deacetylase that is modulated by cellular redox, and has protective effects. The activation of hepatic SIRT1 enhanced fatty acid oxidation by reducing PPARα expression and activity, protecting from diet-induced fatty liver, obesity, and IR (Feige et al. 2008). However, the hepatic Sirt1 activity was decreased in fructose-fed rats, and in human hepatocytes and hepatoma (HepG2) cells treated 25 mM fructose (Rebollo et al. 2014).

Homocysteine levels were found to be higher in patients with stenotic vessels and coronary artery disease scores, and was in fact highest in diabetic patients (Okada et al. 1999). Rats fed a obesogenic diet (high fat, high fructose) had higher homocysteine levels after 5 weeks as compared to chow-fed rats (Oron-Herman et al. 2003; Li et al. 2013).

Therapeutic trials that target fructose-induced NAFLD

We categorized selective therapeutic agents that were used to attenuate fructose-induced fatty liver disease based on their mechanism(s) (Table 2).

Through reducing portal endotoxin levels

This group includes these substances: metformin (dimethylbiguanide) (Lin et al. 2000; Nair et al. 2004; Spruss et al. 2012b), an AMPK-activating drug used in the treatment of T2D and antibiotics (Bergheim et al. 2008), bovine lactoferrin (Ltf), a 76-kDa iron-transporting glycoprotein which is released by neutrophils and mediates anti-inflammatory effects (binds the LPS) (Rivera et al. 2013), bile acids (Volynets et al. 2010), and WAY-362450, a potent synthetic agonist to farnesoid-X-receptor (a member of the nuclear receptor superfamily).

By reducing the expression of lipogenic and inflammatory genes and the oxidative stress

This group includes rapamycin, an inhibitor of mTOR signaling. The "mechanistic target of rapamycin" (mTOR) is a central regulator of a plethora of processes, e.g., cell proliferation and metabolism (Makki et al. 2014). It also includes troglitazone; a new hypoglycemic drug, Levocetirizine; an antihistamine, Lycopene, Carnosine and α-Tocopherol which are antioxidants, and Pentoxifylline; a phosphodiesterase inhibitor.

Through decreasing fructokinase expression

Atorvastatin, a hydroxymethyl-glutaryl-CoA reductase inhibitor, can be used safely in patients with NAFLD and alleviates hepatic steatosis. Atorvastatin decreased the expression of fructokinase in livers of fructose-supplemented rats, reducing the metabolic burden on the liver that is imposed by continuous fructose ingestion (Vilà et al. 2011).

Table 2 Selective therapeutic trials that target fructose-induced NAFLD

Drug/agent	Experimental design	Curative effects
Metformin (Spruss et al. 2012b; Liu et al. 2014a)	C57BL/6J mice were given 30% fructose ±300 mg/kg metformin for 8 weeks	Metformin treatment was associated with a reduction of portal endotoxin level (by serving of tight junction proteins, e.g., occludin in the duodenum), hepatic TG and serum ALT activity
	CD-1 mice were fed with high-fat +15% fructose diet ± 500 mg/kg metformin for 10 weeks	Metformin alleviated IR
Antibiotics (Bergheim et al. 2008)	C57BL/J6 mice drank sugas-sweetened water (30%) ± 92 mg/kg polymyxin B and 216 mg/kg neomycin for 8 weeks	Antibiotics protect against fructose-induced fatty liver and endotoxemia
Lactoferrin (Ltf) (Morishita et al. 2013; Li and Hsieh 2014)	C57BL/6 mice were fed HFCS ± Ltf at 50, 100, or 200 mg/kg for 8 weeks	Ltf treatment dampens hepatic fat accumulation and lipid peroxidation, scavenges LPS in circulation and subsequent expression of inflammatory cytokines, and improves IR
	ICR mice were administered orally with 200 mg/mL/day Ltf for 4 weeks	Ltf reduces visceral fat and liver triglycerides, and thus it had anti-adipogenic activity
Bile acids (Volynets et al. 2010)	C57BL/6J mice treated with chenodeoxycholic and cholic acids (100 mg/kg each) ± a 30%fructose for 8 weeks	Bile acids prevent fructose-induced hepatic steatosis by protection against the fructose-induced translocation of intestinal-bacterial endotoxin
WAY-362450 (Liu et al. 2014b)	C57BL/6J mice, fed 30% fructose were treated ±30 mg/kg WAY for 20 days	WAY reduced serum and hepatic TG levels and attenuated the infiltration of immune cells to the liver and gut LPS translocation
Rapamcyin (Makki et al. 2014; Sapp et al. 2014)	Zebrafish larvae were treated with 4% fructose/glucose ±100 nM rapamycin. A 1 μM tunicamycin or 100 ng/mL valinomycin was added to the treatment as another trail	Rapamycin reversed NASH and decreased the Torc1 activity and phosphorylation of its downstream target. It also reversed oxidative stress-induced hepatic steatosis, and the elevation of lipogenic and inflammatory genes
	C57BL/6JRj mice were reared on high-fat-diet for 5 weeks, then 2 mg/kg rapamycin was *i.p.* administered weekly for 22 weeks	Rapamycin treatment decreased the body weight, protected against IR, and improved the inflammatory profiles of both adipose tissue and liver
Levocetirizine (Shawky et al. 2014)	Male Sprague–Dawley rats were fed 60% fructose ± Levocetirizine for 8 weeks	Levocetirizine ameliorates IR, hepatic steatosis, and lipid peroxidation, and improves glucose tolerance
Carnosine + α-tocopherol (Giriş et al. 2014)	Rats fed 60% fructose with CAR (2 g/L) ± TOC (200 mg/kg, i.m. twice a week) for 8 weeks	CAR + TOC treatment decreased IR, NASH, lipid peroxidation, and pro-oxidant in the liver
Pentoxifylline (PTX) (Azhar and El-Bassossy 2014)	Rats fed HFD and 10% fructose for 12 weeks. PTX was administered (30 mg/kg/day) during the last 4 weeks of the study	PTX alleviates cardiac ischemia and dysfunction following experimental angina in IR through inhibition of the low-grade inflammation
PLCP (Liu et al. 2014a)	CD-1 mice gavaged daily with ethanol extract PLCP for 10 weeks	A diet formula of PLCP alleviates IR, NAFLD, hyperlipidemia, and antioxidant status
MFGEs (Pyo and Lee 2014)	Male Sprague–Dawley rats fed 60% fructose for 16 weeks and orally administered with MFGEs (300 mg/kg/day) or atorvastatin (20 mg/kg) for the last 4 weeks of the study	MFGEs enriched with ubiquinones CoQs exert an antidiabetic effect in T2D by improving IR and hepatic antioxidant enzymes

Table 2 continued

Drug/agent	Experimental design	Curative effects
(−)Epicatechin (EC) (Bettaieb et al. 2014)	Rats fed a chow diet ± EC and 10% fructose for 8 weeks	EC supplementation inhibited events that contribute to IR: increased activity of NADPH oxidase and redox-sensitive signals, expression of NF-κB-regulated proinflammatory cytokines, and ER stress signaling, thus prevented MetS-associated IR
ZSP (Zhao et al. 2014)	Mice fed 20% fructose water ±400 mg/kg ZSP i.g. for 4 weeks	ZSP has hepatoprotective, anti-diabetic and anti-lipidemic effects
Silymarin (SYM) (Prakash et al. 2014)	Wistar rats fed fructose diet for 12 weeks (SYM were given orally during the last 3 weeks)	SYM has anti-hepatotoxic properties: prevented fructose-enhanced hepatic expression of PGC-1α/β and its target transcription factors. It also counteracted the fructose-mediated endothelial dysfunction, metabolic and inflammatory changes
Atorvastatin (Vilà et al. 2011)	Fructose (10% w/v solution) and fructose + atorvastatin (30 mg/kg/day) Sprague–Dawley rats were killed after 2 weeks	Atorvastatin treatment completely abolished histological signs of necroinflammation, reducing the hepatic expression of metallothionein-1 and NFκB binding. Atorvastatin reduced plasma and liver triglyceride concentrations, and increased the hepatic activity of the fatty acid β-oxidation system

PLCP Puerariae radix, Lycium barbarum, Crataegus pinnatifida, and Polygonati rhizome, *MFGEs* monascus-fermented grains, *ZSP* Zizyphus jujube cv. Shaanbeitanzao Polysacharid

Using herbal medications

Several herbs have shown significant beneficial effects in rodent models. For example, plant extracts have protected against fructose-induced metabolic abnormalities. Flavan-3-ol(−)-epicatechin (EC), which belongs to flavonoids, is present in large concentration in fruits and vegetables (Bettaieb et al. 2014). Liquid extract of Monascus-fermented grains enriched with ubiquinones (Coenzyme Qs), an acidic heteropolysaccharide extract (ZSP), derived from *Zizyphus jujube Shaanbeitanzao*, and grape seed extract exhibited anti-diabetic and anti-lipidemic effects (Suwannaphet et al. 2010; Pyo and Lee 2014). Similar pharmacological hepatoprotective effects were found in the active fraction of *Bridelia ferruginea*, the root-bark ethyl acetate (Bakoma et al. 2014), (3,3-dimethylallyl)-halfordinol isolated from leaves of *Aegle marmelos* (Saravanan et al. 2014), *Pleurotus eryngii* (Ren et al. 2014), silymarin extract, and a grape seed Procyanidin extract (Downing et al. 2015).

Nutritional management and conclusions

NAFLD is a disorder mainly associated with obesity (Niklas et al. 2012). In humans, frequent episodes of regular physical activity were significantly lower in the group of NAFLD patients than control subjects (Thuy et al. 2008). Therefore, lifestyle modification is still the first line of the treatment, which shows proven benefits in lowering ALT in NAFLD patients (Thuy et al. 2008). This is analogous to how diet and exercise are the first line of treatment for obesity for both adults and children. Patients with NAFLD should have especial diet recommendation and balanced meals, in order to lose at least 7% of their weight if overweight, reducing caloric intake, mainly at cost of cholesterol and saturated fatty acids (Carvalhana et al. 2012). Weight loss achieved by bariatric surgery decreases liver fat deposits, inflammation and improve insulin sensitivity (Yki-Järvinen 2010; Alwahsh and Ramadori 2015). Fructose over-consumption should be avoided, and soft drinks are discouraged.

In fatty liver patients, improvements in markers of cardiometabolic risk and liver function, as well as body fat were achieved when the patients reduced their intake of fructose from industrialized foods (Volynets et al. 2013). Antioxidant therapy for the treatment of NAFLD, including NASH, has the potential to alleviate oxidative stress and cell death that promote disease progression (Al-Busafi et al. 2012). Many NASH patients have also micronutrient deficiencies and do not have enough antioxidant capacity to prevent synthesis of ROS, resulting in necroinflammation (Lim et al. 2010).

Blocking fructose transporters into the hepatocyte via the GLUT8 hexose transporter may also be a potential mechanism to prevent fructose-induced hepatic steatosis (DeBosch et al. 2014). Impaired hepatic ATP loss attributable to increased dietary fructose consumption underscores the urgent need for increased public awareness of the risks associated with high-fructose consumption (Abdelmalek et al. 2012). Fortunately, metformin and other aforementioned drugs have promising protective effects against fructose-induced fatty liver and endotoxins influx from the intestine.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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