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Journal of Nutritional Biochemistry 20 (2009) 657–662
Journal of Nutritional Biochemistry

REVIEWS: CURRENT TOPICS

Dietary fructose and intestinal barrier: potential risk factor in the pathogenesis of nonalcoholic fatty liver disease

Astrid Spruss, Ina Bergheim*

Department of Nutritional Medicine (180A), University of Hohenheim, Stuttgart, Germany

Received 3 February 2009; received in revised form 17 April 2009; accepted 14 May 2009

Abstract

Worldwide, not only the prevalence of obesity has increased dramatically throughout the last three decades but also the incidences of co-morbid conditions such as diabetes type 2 and liver disease have increased. The 'hepatic manifestation of the metabolic syndrome' is called nonalcoholic fatty liver disease (NAFLD) and comprises a wide spectrum of stages of liver disease ranging from simple steatosis to liver cirrhosis. NAFLD of different stages is found in ~30% of adults and ~20% in the US population. Not just a general overnutrition but also an elevated intake of certain macronutrients such as fat and carbohydrates and herein particularly fructose has been claimed to be risk factors for the development for NAFLD; however, the etiology of this disease is still unknown. The present review outlines some of the potential mechanisms associated with the development of NAFLD and fructose intake with a particular focus on the role of the intestinal barrier functions.

Keywords: NAFLD; Endotoxin; Fructose; Intestinal barrier

1. Introduction

Worldwide, the prevalence of overweight and obesity has increased dramatically throughout the last decades. Overweight and obesity have been identified to be key risk factors for many chronic diseases including cardiovascular diseases, type 2 diabetes, lipid disorders and nonalcoholic fatty liver disease (NAFLD) (for review, see Refs. [1–3]). NAFLD comprises a wide spectrum of liver diseases that develop in the absence of significant alcohol consumption (<20 g ethanol/day) or other known causes of steatosis (*e.g.*, abuse of drugs or toxins). The earliest and most common type of this liver disease is simple steatosis, which has long been thought to be a relatively benign state of liver injury. However, results of human studies indicate that fatty livers are more vulnerable to injury from various causes [4] and can progress to steatohepatitis, increasing the probability of further liver-related morbidity and mortality [5]. Despite intense research, numerous questions remain unanswered and therapeutic options are still limited. The current review will focus primarily on data from our lab and elsewhere examining the potential role of dietary fructose intake, bacterial overgrowth and the intestinal barrier in the onset and development of NAFLD. Finally, the role of the influence of dietary fructose intake on intestinal barrier and permeability will be discussed.

2. Added sugar and fructose intake

The main sugars consumed in diet are glucose, fructose and sucrose. Sucrose is a disaccharide composed of equal parts of fructose and glucose. In the United States, high-fructose corn syrup (HFSC), containing 42–90% fructose,

Abbreviations: GLUT-5, glucose transporter 5; HFSC, high-fructose corn syrup; HGF, hepatocyte growth factor; LBP, lipopolysaccharide binding protein; MTP, microsomal triglyceride transport protein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFκB, nuclear factor kappaB; PAI-1, plasminogen activator inhibitor 1; TLR-4, toll-like receptor 4; TNFα, tumor necrosis factor alpha; VLDL, very-low-density lipoprotein.

* Corresponding author. Hohenheim University (180A), Fruwirthstrasse 12, 70599 Stuttgart, Germany. Tel.: +49 711 4592 4102; fax: +49 711 4592 4343.

E-mail address: bergheim@uni-hohenheim.de (I. Bergheim).

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doi:10.1016/j.jnutbio.2009.05.006

has increasingly replaced refined sugar (sucrose) in many foods and most sweetened beverages [6,7]. Outside the United States, HFCS has not been used extensively; however, in more recent years, in Europe sucrose is more and more being replaced by fructose–glucose syrup containing at least 50% fructose or fructose syrup, too. Based on currently available evidence, it has been concluded that HFCS does not contribute to diseases (*e.g.*, obesity or diabetes type 2) any differently than sucrose does (for review, see Ref. [8]).

In recent reviews, it was reported that the average per capita intake of added sugars in the US has increased from ~64 kg/year in 1970 to ~80 kg/year in 2000 [9,10]. Furthermore, a recently published analysis of data from the NHANES III study using 24-h recalls to assess dietary intake (data collection 1988–1994) [11] further revealed an almost 50% increase in fructose intake from that reported by Park and Yetley [12] (55 *vs.* 37 g/days) who analysed data obtained between 1977 and 1978. In an ecological analysis, in which national data from 1909 to 1997 were used, a continuous increase in intake and a strong association between an increased consumption of refined carbohydrates and the prevalence of diabetes were reported for the United States [5]. Furthermore, in this study, a correlation between the increased prevalence of type 2 diabetes and the increasing per capita percentage of carbohydrate intake from corn syrup was found [5]. In line with these findings, a recently published study from Germany reported an association between fruit juice and soft drink intake and the risk of developing obesity in adolescents [13]. Results of studies of our own group [14] and other groups [15–17] further suggest that a diet rich in carbohydrates and herein particularly fructose may also be associated with the development of NAFLD and may increase the odds of developing the later stages of the disease [*e.g.*, nonalcoholic steatohepatitis (NASH)]. In support of these human studies, we found in animal studies that a diet rich in glucose (*e.g.*, 30% glucose solution *ad libitum* for 8 weeks) can result in overweight in mice; however, contrary to the findings for the *ad libitum* feeding of 30% fructose solution, the diet enriched in glucose did not cause any significant accumulation of fat in the liver [18]. Furthermore, in a pilot study, we found that total carbohydrate intake of patients with NAFLD (*e.g.*, simple steatosis to NASH with beginning fibrosis) did not differ from that of controls; however, in this study, fructose intake of patients with different stages of NAFLD was markedly higher than that of controls. This is also in line with the findings of Zelber-Sagi et al. [19], who reported in a larger cohort (n=349) that total intake of carbohydrates of patients with NAFLD did not differ from that of healthy controls; rather, the dietary pattern (*e.g.*, consumption of different foods and beverages) significantly differed between patients with NAFLD and controls. In this study, the authors found that patients with NAFLD consumed markedly larger amounts of sugar-sweetened soft drinks than disease-free controls. Ouyang et al. [16], who assessed dietary intake of HFCS originating from different sweets (*e.g.*, jelly beans) and sugar-containing beverages, reported that daily consumption of these foods and drinks was ~2.1-fold higher in patients with NAFLD than in controls, resulting in a significantly higher intake of fructose in patients with NAFLD in comparison to controls. Furthermore, Assy et al. [15] concluded from their recently published study, in which they compared dietary intake of food and soft drinks of 31 patients with NAFLD but without classical risk factors (*e.g.*, diabetes, obesity, hyperlipidemia, or hypertension) with 30 healthy controls, that consumption of sugar-sweetened beverages is the most common risk factor for the fatty infiltration of the liver in these patients. Taken together, these data suggest that an increased intake of fructose may be a risk factor for the development of NAFLD in humans.

3. Fructose metabolism in the liver

Fructose is readily absorbed and transported through enterocytes to the portal bloodstream by a fructose-specific hexose transporter (GLUT5), expressed on both the apical lumen facing border of the intestinal mucosa and the basolateral enterocyte membranes [20] (see Fig. 1). From the portal plasma, fructose is then efficiently taken up by the liver so that only little escapes the hepatic metabolism and enters the systemic circulation. In the liver, fructose is phosphorylated by fructokinase to fructose-1-phosphate, which is metabolised to the triose phosphates glyceraldehydes and dihydroxyacetone phosphate. As fructose is metabolised through this route in the liver, its metabolism bypasses the main rate-limiting step in glycolysis, which is catalysed by phosphofructokinase. Thus, while glucose metabolism is tightly regulated through the allosteric inhibition of phosphokinase by citrate and ATP, fructose can continuously and uncontrollably enter the glycolytic/gluconeogenetic pathway resulting in the production of glucose, glycogen, lactate and pyruvate. Pyruvate and lactate are both precursors of the formation of acyl-glycerol molecules, which, when large amounts of fructose are consumed, can contribute to an increased formation of triglycerides and, subsequently, production of very-low-density lipoprotein (VLDL). However, even with increased *de novo* lipogenesis, steatosis should only occur if storage of the lipids is increased due to abnormal exportation out of the hepatocyte or decreased utilization of the fatty acids in β-oxidation, suggesting that other mechanisms may also be involved in the deleterious effects of fructose on liver.

4. Fructose and hepatic gene transcription

Until recently, it was thought that glycolytic and lipogenic gene transcription is induced mainly by insulin through transcription factors such as the sterol regulatory element

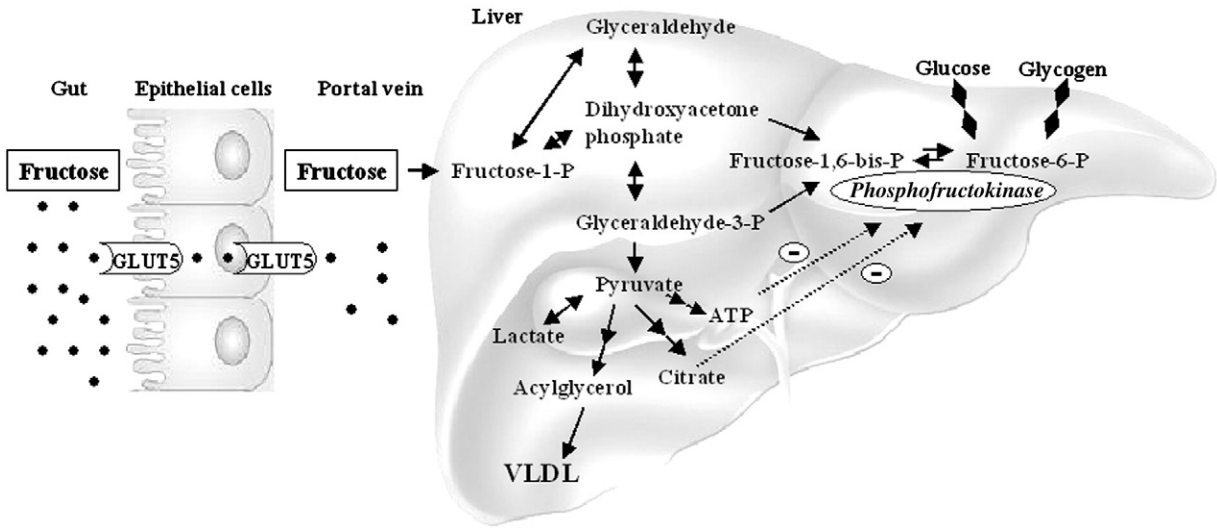

Fig. 1. Fructose uptake and its metabolism in the liver. After mucosal absorption by glucose transporter (GLUT-) 5, fructose is transported to the liver via the portal blood and phosphorylated to fructose-1-phosphate (-P), which is then divided into glyceraldehyde and dihydroxyacetone-phosphate. Thus, the glycolytic pathway is being entered at the triose phosphate level of dihydroxyacetone-phosphate and glyceraldehyde-3-phosphate thereby bypassing the phosphofructokinase-controlled step of glycolysis, which is limited by a negative feedback reaction via citrate and ATP.

binding protein 1-c (SREBP-1c). Indeed, high-fructose diets have been linked to insulin resistance repeatedly (for review, see Refs. [21–23]) and it has been shown that dietary fructose, *per se*, activates lipogenesis at least partly through inducing expression of SREBP-1 [24]. Although there is evidence linking the induction of SREBP-1 to fructose-induced lipogenesis *in vivo*, the mechanisms responsible for fructose-induced alterations in SREBP-1c transcription have not yet been fully understood. Results of recent animal-based studies implicate that the peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 (PGC-1) β plays a pivotal role in fructose-induced lipogenesis through mechanisms involving insulin resistance [25]. Indeed, PGC-1β has been shown to activate the expression of genes involved in lipogenesis and triglyceride secretion directly through coactivating SREBPs [26]. Furthermore, Takemoto et al. [27] identified an X-chromosome-linked RNA binding motif protein (RBMX) using the MALDI-TOF MASS technique as being involved in the regulation of the activation of the SREBP-1c promotor induced by high-fructose feeding in rodents. However, the exact mechanisms underlying this regulation remain to be determined. The recognition that carbohydrates, independent of insulin, also induced glycolytic and lipogenic gene expression has led to the discovery of the carbohydrate response element binding protein (ChREBP), a nuclear transcription factor that not only is responsive to glucose but has also been suggested to mediate the effects of fructose [28]. Indeed, it was recently shown by Rodriguez-Calvo et al. [29] that chronic intake of fructose (*e.g.*, 50% of total caloric intake) can lead to an activation of ChREBP in rats and, subsequently, an induction of glycerol-3-phosphate acyltransferase (Gpat1) in the liver. Interestingly, in this study, the concomitant treatment with statin atorvastatin blunted the effects of fructose on ChREBP probably through protein kinase A-dependent pathways [29]. Taken together, these data suggest that fructose may, either through direct interaction or indirectly through causing insulin resistance, interact with nuclear transcription factors subsequently leading to alterations in the expression of genes involved in lipogenesis and glycolysis in the liver.

5. Bacterial overgrowth, intestinal barrier and NAFLD

Results of several animal and human studies suggest that similar to alcoholic liver disease (for review, see Ref. [30]) small intestinal bacterial overgrowth may be involved in the pathogenesis of NAFLD. For instance, in the 1980s, NASH was described as a rather common complication of jejunoileal bypass surgeries performed for weight loss in morbidly obese patients, which could be reversed when patients were treated with metronidazole [31]. Furthermore, NASH-associated liver transplantation was required for several patients after jejunoileal bypass surgery [32]; interestingly, NASH recurred rapidly following transplantation further supporting the hypothesis that small bacterial overgrowth may contribute to the development of NAFLD. Bode et al. [33] were among the first to report that patients with nonalcoholic cirrhosis suffer from endotoxemia. In accordance with these findings of Bode et al. [33], Soza et al. [34] and Wigg et al. [35] report that patients with NASH had a higher prevalence of small intestinal bacterial overgrowth and prolonged orocecal transit time, as determined by lactulose breath test. Recently, we and others reported that plasma endotoxin levels were significantly elevated in patients with different stages of NAFLD (ranging from simple steatosis to steatohepatitis with beginning fibrosis) [14,36] and that this was associated with increased intestinal

permeability [36]. In the study of Ruiz et al. [37], it was further shown that, the levels of lipopolysaccharide binding protein (LBP) in plasma of patients with NAFLD were elevated and that the LBP concentrations were even further increased in the plasma of patients with NASH. The increased levels of LBP in the plasma of patients with NASH were associated with a markedly increased expression of tumor necrosis factor (TNF-) α in liver tissue [37]. In line with these findings, we recently showed that the increased plasma endotoxin levels found in humans with NAFLD of various stages are accompanied by an induction of the endotoxin receptor toll-like receptor (TLR-) 4 in the liver [14]. The role of endotoxin in the pathogenesis of NAFLD is also supported by the results of several animal studies. For instance, Rivera et al. [38] found that TLR-4 mutant mice fed a methionin-/cholin-deficient diet are protected from the development of NASH associated with this diet. Furthermore, results of animal studies performed in an animal model of genetically obese animals (ob/ob mice) [39] suggest that the increased intestinal permeability and plasma endotoxin levels found in ob/ob mice with NASH are associated with a loss of the tight junction protein occludin.

Under anaerobic conditions, the bacterial metabolism of pyruvate, which is produced during the breakdown of carbohydrates, generates acetaldehyde, which can then be further reduced to form ethanol [40,41]. This metabolic fate of carbohydrates is favoured when there is intestinal overgrowth of bacteria or yeast [6,42,43] or if carbohydrates are consumed excessively [44]. Indeed, it was shown before in animal studies that intragastric administration of sucrose in rats with a jejunal self-filling diverticulum (blind loop) can result in a marked increase of acetaldehyde and ethanol levels in portal plasma. Furthermore, the results of animal and human studies from Cope et al. [45] and Nair et al. [46] suggest that both obese mice and overweight female patients with NASH exhale ethanol in their breath even in the absence of ethanol ingestion. Treatment with antibiotics reduced breath ethanol content markedly in ob/ob mice [45]. Taken together, these data suggest that intestinal bacterial overgrowth and production of ethanol along with an increased intestinal permeability may contribute to the genesis of NAFLD. However, causes of the alteration of the bacterial flora and increased intestinal permeability have not yet been clarified.

6. Dietary fructose intake, NAFLD and the intestinal barrier

Results of several recent studies suggest that an increased intake of dietary fructose may be associated with the development of NAFLD [14–16]. However, as steatosis due to increased fructose intake should only occur if storage of the lipids is increased due to abnormal exportation out of the hepatocyte or decreased utilization of the fatty acids in β-oxidation, other factors besides the continuous and uncontrollable entry of fructose into the glycolytic pathway may be involved in the fructose-induced damage. Indeed, it has been repeatedly suggested by the results of animal studies that dietary fructose facilitates oxidative damage in various tissues [18,47–51]. An increased formation of reactive oxygen species has been repeatedly claimed as a major contributor of the genesis of liver damage in humans (for review, see Ref. [52]); however, up to now, underlying mechanisms (*e.g.*, dietary factors) leading to the imbalance in the oxidant/antioxidant system in the liver have not yet been fully understood. Our group and others found various markers of the formation of reactive oxygen species (*e.g.*, formation of 4-hydroxynonenal adducts, malondialdehyde, thiobarbituric acid-reactive substances) to be markedly elevated in rodents chronically consuming fructose orally for several weeks (4–8 weeks, depending on the experiment's setting) [18,47,51,53], while antioxidative parameters (*e.g.*, paraoxonase, α-tocopherol catalase, Cu–Zn superoxide dismutase, gluthathione peroxidase) were repeatedly found to be decreased [47,53–55]. Furthermore, in a recently published human study in which it was shown that intake of sugar-sweetened beverages was the most common risk factor for hepatic fat accumulation in NAFLD patients without any classical risk factors (*e.g.*, obesity, diabetes type 2), levels of malondialdehyde, which is a marker of oxidative stress, were markedly elevated [15]. Interestingly, the protective effects on the development of NAFLD in several animal studies of various nutraceuticals and drugs (*e.g.*, probiotics, thymosin α-1, nonresorbable antibiotics, captopril, bezafibrate, oligofructose, spice mixture, fenofibrate) given concomitantly

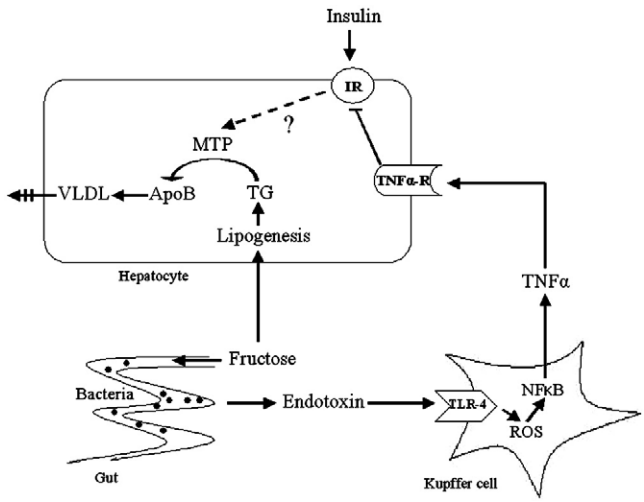

Fig. 2. Possible molecular mechanism involved in the development of fructose-induced NAFLD. Besides bypassing the phosphofructokinase-controlled step of glycolysis (see Fig. 1), chronic intake of fructose may lead to bacterial overgrowth, increased intestinal permeability and, subsequently, elevated endotoxin levels in the portal blood as well as to an activation of Kupffer cells, increased formation of reactive oxygen species (ROS) via TLR-4-dependent signalling pathways and an NFκB-dependent induction of TNF-α. TNF-α can then cause insulin resistance (IR) in hepatocytes, which in turn may alter hepatic triglyceride (TG) secretion VLDLs.

while animals were fed a fructose-enriched diet were always associated with an improvement in or protection against oxidative damage [15,18,24,47,49,51,53,55]. However, in most of these studies, the intervention was targeting neither fructose metabolism nor the oxidative/antioxidative system in the liver. In line with this observation, we recently reported that in mice treated with nonresorbable antibiotics, fructose-induced liver damage is reduced by approximately 50%. The protective effect of the antibiotic treatment in this study was associated with a marked decrease in portal endotoxin levels and the hepatic activation of IκB as well as TNFα expression in these animals. Together with the findings of Suganthi et al. [51] and Busserolles et al. [49], who reported that concomitant treatment of fructose-fed mice with pro- and prebiotics, respectively, protects rodents from fructose-induced liver damage, these data support the hypothesis that fructose damages the liver, at least in part, through mechanisms involving intestinal bacterial overgrowth and increased intestinal permeability as well as endotoxemia (see Fig. 2). In support of this hypothesis, it has been shown repeatedly that in various settings of liver damage where bacterial overgrowth, increased intestinal permeability and increased translocation of bacterial endotoxin are involved in the pathogenesis, an activation of Kupffer cells and increased formation of reactive oxygen species can mediate the release of proinflammatory cytokines such as TNFα through nuclear factor κB (NFκB)-dependent pathways (for review, see Ref. [56]). Furthermore, results of human and animal studies of our own group suggest that, similar to the findings of alcoholic liver disease [57], secretion of hepatic triglycerides may be impaired through mechanisms involving a TNFα-/insulin-dependent induction of plasminogen activator inhibitor (PAI-) 1 and subsequent down-regulation of the hepatocyte growth factor (HGF)/cMet signalling cascade involved in the regulation of microsomal triglyceride transport protein (MTP) [14]. However, underlying mechanisms such as how fructose leads to bacterial overgrowth and/or increases intestinal permeability remain to be determined.

7. Summary and Conclusion

Consumption of fructose in the diet has increased markedly throughout the last decades paralleling the increased incidence of obesity and diabetes, two of the main risk factors of NAFLD. Indeed, results of several recent human studies suggest that patients with NAFLD and herein particularly those with more severe liver damage (*e.g.*, NASH) consume more carbohydrates and herein especially fructose in their diet than healthy controls. However, although much is known about hepatic fructose metabolism, knowledge on the role of fructose in the development of liver disease is still limited. Results of animal studies suggest that the genesis of fructose-induced NAFLD is associated with an increased formation of reactive oxygen species and an imbalance of the oxidant/antioxidant system in the liver. Furthermore, it has recently been suggested by the results of studies performed in rodents that chronic intake of fructose may, similar to alcohol, cause intestinal bacterial overgrowth, increased intestinal permeability and translocation of bacterial endotoxins into the portal plasma which may result in activation of hepatic Kupffer cells and subsequently add to the development of NAFLD (see Fig. 2). However, further studies will be necessary to determine the underlying mechanisms and the possible new therapeutic targets (*e.g.*, fructose avoidance diet, probiotics, prebiotics).

Acknowledgments

The authors would like to acknowledge the Bergheim lab and the support from the Federal Ministry of Education and Research (Az: 0315084) and the German Research Foundation (BE2376/4-1).

References

[1] Olufadi R, Byrne CD. Clinical and laboratory diagnosis of the metabolic syndrome. J Clin Pathol 2008;61:697–706.
[2] Xing J, Chen JD. Alterations of gastrointestinal motility in obesity. Obes Res 2004;12:1723–32.
[3] Younossi ZM. Review article: current management of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2008;28:2–12.
[4] Adams LA, Lymp JF, St SJ, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113–21.
[5] Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. Am J Clin Nutr 2004;79:774–9.
[6] Hanover LM, White JS. Manufacturing, composition, and applications of fructose. Am J Clin Nutr 1993;58:724S–32S.
[7] US Department of Agriculture. The food pyramid. US Dept of Agriculture; 1992.
[8] Forshee RA, Storey ML, Allison DB, et al. A critical examination of the evidence relating high fructose corn syrup and weight gain. Crit Rev Food Sci Nutr 2007;47:561–82.
[9] Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr 2004;79:537–43.
[10] Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. Am J Clin Nutr 2002;76:911–22.
[11] Vos MB, Kimmons JE, Gillespie C, Welsh J, Blanck HM. Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. Medscape J Med 2008;10:160.
[12] Park YK, Yetley EA. Intakes and food sources of fructose in the United States. Am J Clin Nutr 1993;58:737S–47S.
[13] Libuda L, Alexy U, Sichert-Hellert W, et al. Pattern of beverage consumption and long-term association with body-weight status in German adolescents—results from the DONALD study. Br J Nutr 2008;99:1370–9.
[14] Thuy S, Ladurner R, Volynets V, et al. Nonalcoholic fatty liver disease in humans is associated with increased plasma endotoxin and plasminogen activator inhibitor 1 concentrations and with fructose intake. J Nutr 2008;138:1452–5.
[15] Assy N, Nasser G, Kamayse I, et al. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. Can J Gastroenterol 2008;22:811–6.

[16] Ouyang X, Cirillo P, Sautin Y, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol 2008;48:993–9.
[17] Solga S, Alkhuraishe AR, Clark JM, et al. Dietary composition and nonalcoholic fatty liver disease. Dig Dis Sci 2004;49:1578–83.
[18] Bergheim I, Weber S, Vos M, et al. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. J Hepatol 2008;48:983–92.
[19] Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. J Hepatol 2007;47:711–7.
[20] Castello A, Guma A, Sevilla L, et al. Regulation of GLUT5 gene expression in rat intestinal mucosa: regional distribution, circadian rhythm, perinatal development and effect of diabetes. Biochem J 1995; 309(Pt 1):271–7.
[21] Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. Nutr Rev 2005;63: 133–57.
[22] Laville M, Nazare JA. Diabetes, insulin resistance and sugars. Obes Rev 2009;10(Suppl 1):24–33.
[23] Stanhope KL, Havel PJ. Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance. Curr Opin Lipidol 2008;19:16–24.
[24] Nagai Y, Nishio Y, Nakamura T, Maegawa H, Kikkawa R, Kashiwagi A. Amelioration of high fructose-induced metabolic derangements by activation of PPARalpha. Am J Physiol Endocrinol Metab 2002;282: E1180–90.
[25] Nagai Y, Yonemitsu S, Erion DM, et al. The role of peroxisome proliferator-activated receptor gamma coactivator-1 beta in the pathogenesis of fructose-induced insulin resistance. Cell Metab 2009;9:252–64.
[26] Lin J, Yang R, Tarr PT, et al. Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP. Cell 2005;120:261–73.
[27] Takemoto T, Nishio Y, Sekine O, et al. RBMX is a novel hepatic transcriptional regulator of SREBP-1c gene response to high-fructose diet. FEBS Lett 2007;581:218–22.
[28] Yamashita H, Takenoshita M, Sakurai M, et al. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. Proc Natl Acad Sci U S A 2001;98:9116–21.
[29] Rodriguez-Calvo R, Barroso E, Serrano L, et al. Atorvastatin prevents carbohydrate response element binding protein activation in the fructose-fed rat by activating protein kinase A. Hepatology 2009;49: 106–15.
[30] Purohit V, Bode JC, Bode C, et al. Alcohol, intestinal bacterial growth, intestinal permeability to endotoxin, and medical consequences: summary of a symposium. Alcohol 2008;42:349–61.
[31] Drenick EJ, Fisler J, Johnson D. Hepatic steatosis after intestinal bypass—prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. Gastroenterology 1982;82:535–48.
[32] Kim WR, Poterucha JJ, Porayko MK, Dickson ER, Steers JL, Wiesner RH. Recurrence of nonalcoholic steatohepatitis following liver transplantation. Transplantation 1996;62:1802–5.
[33] Bode C, Kugler V, Bode JC. Endotoxemia in patients with alcoholic and non-alcoholic cirrhosis and in subjects with no evidence of chronic liver disease following acute alcohol excess. J Hepatol 1987;4:8–14.
[34] Soza A, Riquelme A, Gonzalez R, et al. Increased orocecal transit time in patients with nonalcoholic fatty liver disease. Dig Dis Sci 2005;50: 1136–40.
[35] Wigg AJ, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG. The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis. Gut 2001; 48:206–11.
[36] Farhadi A, Gundlapalli S, Shaikh M, et al. Susceptibility to gut leakiness: a possible mechanism for endotoxaemia in non-alcoholic steatohepatitis. Liver Int 2008;28:1026–33.
[37] Ruiz AG, Casafont F, Crespo J, et al. Lipopolysaccharide-binding protein plasma levels and liver TNF-alpha gene expression in obese patients: evidence for the potential role of endotoxin in the pathogenesis of non-alcoholic steatohepatitis. Obes Surg 2007;17:1374–80.
[38] Rivera CA, Adegboyega P, van RN, Tagalicud A, Allman M, Wallace M. Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. J Hepatol 2007; 47:571–9.
[39] Brun P, Castagliuolo I, Di V L, et al. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2007;292: G518–25.
[40] Logan BK, Jones AW. Endogenous ethanol 'auto-brewery syndrome' as a drunk-driving defence challenge. Med Sci Law 2000;40:206–15.
[41] McManus IR, Contag AO, Olson RE. Characterization of endogenous ethanol in the mammal. Science 1960;131:102–3.
[42] Baraona E, Julkunen R, Tannenbaum L, Lieber CS. Role of intestinal bacterial overgrowth in ethanol production and metabolism in rats. Gastroenterology 1986;90:103–10.
[43] Mezey E, Imbembo AL, Potter JJ, Rent KC, Lombardo R, Holt PR. Endogenous ethanol production and hepatic disease following jejunoileal bypass for morbid obesity. Am J Clin Nutr 1975;28: 1277–83.
[44] Hunnisett A, Howard J, Davies S. Gut fermentation (or auto-brewery) syndrome. A new clinical test with initial observations and discussion of clinical and biological implications. J Nutr Med 1990;1:33–8.
[45] Cope K, Risby T, Diehl AM. Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. Gastroenterology 2000;119:1340–7.
[46] Nair S, Cope K, Risby TH, Diehl AM. Obesity and female gender increase breath ethanol concentration: potential implications for the pathogenesis of nonalcoholic steatohepatitis. Am J Gastroenterol 2001; 96:1200–4.
[47] Armutcu F, Coskun O, Gurel A, et al. Thymosin alpha 1 attenuates lipid peroxidation and improves fructose-induced steatohepatitis in rats. Clin Biochem 2005;38:540–7.
[48] Busserolles J, Gueux E, Rock E, Mazur A, Rayssiguier Y. Substituting honey for refined carbohydrates protects rats from hypertriglyceridemic and prooxidative effects of fructose. J Nutr 2002;132:3379–82.
[49] Busserolles J, Gueux E, Rock E, Demigne C, Mazur A, Rayssiguier Y. Oligofructose protects against the hypertriglyceridemic and pro-oxidative effects of a high fructose diet in rats. J Nutr 2003;133: 1903–8.
[50] McDonald RB. Influence of dietary sucrose on biological aging. Am J Clin Nutr 1995;62:284S–92S.
[51] Suganthi R, Rajamani S, Ravichandran MK, Anuradha CV. Effect of food seasoning spices mixture on biomarkers of oxidative stress in tissues of fructose-fed insulin-resistant rats. J Med Food 2007;10: 149–53.
[52] Farrell GC, Teoh NC, McCuskey RS. Hepatic microcirculation in fatty liver disease. Anat Rec (Hoboken) 2008;291:684–92.
[53] Ackerman Z, Oron-Herman M, Rosenthal T, et al. Effects of amlodipine, captopril, and bezafibrate on oxidative milieu in rats with fatty liver. Dig Dis Sci 2008;53:777–84.
[54] Cavarape A, Feletto F, Mercuri F, Quagliaro L, Daman G, Ceriello A. High-fructose diet decreases catalase mRNA levels in rat tissues. J Endocrinol Invest 2001;24:838–45.
[55] Yadav H, Jain S, Prasad GB, Yadav M. Preventive effect of diabegon, a polyherbal preparation, during progression of diabetes induced by high-fructose feeding in rats. J Pharmacol Sci 2007;105:12–21.
[56] Bode C, Bode JC. Activation of the innate immune system and alcoholic liver disease: effects of ethanol per se or enhanced intestinal translocation of bacterial toxins induced by ethanol? Alcohol Clin Exp Res 2005;29:166S–71S.
[57] Bergheim I, Guo L, Davis MA, et al. Metformin prevents alcohol-induced liver injury in the mouse: Critical role of plasminogen activator inhibitor-1. Gastroenterology 2006;130:2099–112.