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FRUCTOSE, SUGAR CONSUMPTION, AND METABOLIC DISEASES

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Abstract: There is evidence that high-fructose diets can lead to the development of obesity, insulin resistance, and dyslipidemia in rodent models. However, the role of fructose in the recent increase in prevalence of metabolic diseases in humans remains heavily debated. Several epidemiological studies show a positive correlation between consumption of added sugar, fructose, or sweetened beverages on one hand, and obesity and metabolic disorders on the other hand; such studies do not demonstrate a causal relationship, however. Fructose, as an energy substrate constituting, on average, 10% total energy intake, contributes to the excess energy intake that causes obesity; whether this is specifically related to fructose having no satiating effect remains to be demonstrated, however. Most short-term intervention studies show that a high-fructose diet can, over a short period of time, increase fasting and post-prandial plasma triglyceride concentrations, and increase small, dense LDL particles, and thus may confer an increased cardiovascular risk. They also show that fructose increases endogenous glucose production and enhances the glycemic response to oral glucose, suggesting hepatic insulin resistance. In contrast, there is little, or only preliminary, evidence that fructose plays an important, pathogenic role in the development of muscle insulin resistance, diabetes mellitus, nonalcoholic steatohepatitis, hyperuricemia, or high blood pressure.

31.1 INTRODUCTION

Fructose is a hexose that is naturally present, together with glucose and sucrose, in fruits and honey. The presence of specific enzymes metabolizing fructose indicates that humans and most mammals developed the ability to use fructose as a metabolic substrate at some point during evolution, and hence that it most likely conferred an advantage for survival. However, the overall consumption of fructose is likely to have been relatively low until the Middle Ages due to the limited amount of fruits, berries, and honey in the wild, and to the difficulty in gathering these foods in important quantities. Sugar was available in Asia, however, where sugar cane was growing, and in the Middle East through trading with Asian countries. Consumption of sugar in Europe started only after the crusades, when crusaders became acquainted with this product. Sugar at this time was scarce and expensive, and was therefore used in very small amounts and considered mainly as a spice. The availability of sugar increased during the colonial area, and its consumption was boosted by the introduction of new beverages such as tea, coffee, or chocolate. At the

Metabolic Syndrome and Neurological Disorders, First Edition. Edited by Tahira Farooqui and Akhlaq A. Farooqui.

turn of the twentieth century, its consumption further increased due to technological development for the production of sodas, ice cream, and chocolate bars. Since then, it has continuously increased in Europe and North America, rising from a daily consumption of 20–30 g at the beginning of the twentieth century, to a staggering current figure of 140–150 g/person/day in Europe, North and South America, and Oceania. Recent estimations in the United States indicate that sugar represents, on average, 20% of total daily energy intake, and there is no doubt that presently we have the highest sugar consumption in human history [1, 2].

Initially, the major source of sugar was sugar cane, which, during the colonial area, was extensively cultivated in South America, the West Indies, and Asia. Since the eighteenth and twentieth centuries sugar beets have been grown in Europe and North America, respectively, to secure indigenous sources of sugar. Both sugar cane and sugar beets naturally produce sucrose, which is a disaccharide made up of one molecule of glucose linked to one molecule of fructose. Sugar cane and beet sugar were the main dietary sources of fructose until the 1970s. However, in the 1960s, technology was developed that allowed enzymatic isomerization of glucose to fructose at the industrial level. This technology was rapidly adopted by the North American corn wet milling industry to prepare high-fructose corn syrup (HFCS). This product is obtained from the sequential hydrolysis of corn starch—first to oligosaccharides ("traditional" glucose-based corn syrup) and then to glucose/residual oligosaccharides—followed by the isomerization of glucose to fructose to provide fructose/glucose syrup. The two preparations of corn glucose/oligosaccharides and fructose/glucose are then blended in various proportions to yield HFCS containing 42% or 55% fructose and 45% or 58% glucose/maltose/oligosaccharides [3]. Due to its lower cost of preparation, its sweetness equivalent to sugar, and its functional properties (stability in acidic foods and beverages, increased shelf life via moisture and microbial spoilage control, browning and soft texture in baked goods, and reduced crystallization), the use of HFCS gradually increased in North America until 1999 [4]. HFCS represented roughly one-third of added sugar consumption in United States in 2004 [5], but remained very low in most other parts of the world, and worldwide sucrose consumption exceeds high-fructose syrups by a ratio of 10:1. Besides corn, high-fructose syrup can be made from a variety of starch-rich sources like wheat, potato, rice, and tapioca using the same technology [6].

There has been a recent controversy regarding a potential role of HFCS in the development of obesity. This was based on the observation that both the consumption of HFCS and the prevalence of obesity increased markedly between 1970 and 2000 [4]. The hypothesis that HFCS was a cause for obesity gained a large popularity in the lay public, in part due to the fact that the product's appellation suggested that it provided substantially more fructose than did sucrose. HFCS is made up of glucose and fructose in roughly the same proportion of sucrose, with the only difference that these hexoses are in a free form in HFCS, whereas they are linked by a glycosidic bond in sucrose. Although few studies are available, there is presently no data indicating that HFCS exerts different metabolic effects than sucrose, nor that it may exert more deleterious effects [7, 8].

31.2 FOOD ENERGY: THE ROLE OF THE LIVER IN PROCESSING ENERGETIC SUBSTRATES

The paleolithic diet was essentially composed of animal fat, meat and fish protein, and starch from whole grains [9, 10]. Sucrose and lactose are therefore dispensable energy substrate for adults that have become present in substantial amounts in our diets relatively late in human history.

In the human gut, starch is digested to maltose and oligosaccharides under the actions of salivary and pancreatic amylases, and then split into glucose by the enzymes maltase and isomaltase located at the surface of the intestinal cells. Starch is therefore finally released into the circulation as glucose. Dietary fat is essentially constituted by trigylcerides and phospholipids, which are absorbed and packaged into chylomicrons in the enterocytes, and released into the lymphatic circulation, thus bypassing the liver to be directly released into the systemic circulation. The triglycerides transported with chylomicrons are essentially stored in adipose tissue, from where they can be released into the systemic circulation

as non-esterified fatty acids. Part of the fatty acids released from adipose tissue can be taken up by the liver, where they can be converted into ketone bodies [11, 12]. Most cells of the organism can use glucose or fatty acids and ketone bodies as energy substrate, according to their relative availability. This reliance on only two energy fuels spares highly specialized cells the need to synthesize the numerous enzymes required to oxidize every single nutritional substrate.

Dietary proteins are split into amino acids and small peptides in the gut, and the amino acids are then absorbed by the enterocytes and released into the portal blood. Blood amino acids are made available for protein synthesis in all the organs and tissues of the organism. In contrast to glucose and fatty acids, however, blood amino acids are not a source of energy readily available, because most cells are unable to oxidize them (except for branched-chain amino acids that can be oxidized in skeletal muscle) for the purpose of energy production. Therefore, amino acids constitute a "special" energy fuel, which is present in our diet but not directly available for energy.

Like amino acids, fructose (present in fruits and sugar), galactose (present in the lactose molecule in milk), and alcohol (another dispensable nutrient often present in adults' diet in Western countries) cannot be used directly by the most cells of our organism. These products nonetheless are digested and absorbed by the gastro-intestinal tract, sometimes with specific enzymes (sucrase-isomaltase for sugar, lactase for lactose) and transporters (GLUT5 for fructose), which indicates that the human organism has evolved to be able to use these nutrients.

Once absorbed, amino acids, fructose, galactose, and alcohol are released into the portal circulation, and will therefore reach the liver before being eventually released into the systemic circulation. One important metabolic function of the liver is to convert these special energy fuels into energy substrates that can be used by extra-hepatic cells. Amino acids, fructose, and galactose are thus essentially converted into glucose (and to a lesser extent into lactate, which enters glucose metabolism beyond glycolysis), whereas alcohol is released as acetate, which is a direct precursor of acetyl-CoA. For amino acids, the simultaneous stimulation of hepatic gluconeogenesis and ureagenesis further prevents the release of potentially toxic ammonium in the systemic circulation [13]. Very schematically, the liver can be viewed as a "metabolic plant" converting unusual substrates into substrates readily used by all cells, and at the same time delaying the delivery of substrates to extra-hepatic cells (Fig. 31.1).

31.3 SPLANCHNIC FRUCTOSE METABOLISM

Sucrose represents, by far, the most important source of fructose in our diet (with the exception of North American diets, in which HFCS may represent nearly one-third of total fructose intake). Sucrose is split into glucose and fructose by the enzyme sucrase-isomaltase present in the brush border of the proximal small bowel. Sucrose hydrolysis by sucrase-isomaltase appears to be a rapid process [14], and is generally thought not to be rate-limiting for the absorption of sugar-derived glucose and fructose, but detailed analysis of the kinetics of the sucrose reaction are still lacking. After sucrose hydrolysis, glucose is transported into the enterocyte by a sodium-glucose co-transporter (SGLT-1) located at the apical side of the enterocyte. This energy-dependent process is driven by the continuous extrusion of Na^+ out of the cell by the enzyme Na-K ATPase, present in the basolateral membrane of the enterocytes. This maintains a positive concentration gradient between luminal and intracellular Na^+, thus facilitating the transport of glucose. In contrast, fructose is absorbed independently of Na^+ by a specific transporter, GLUT5, which is present in the apical membrane of enterocytes. Glucose and fructose are subsequently released into the blood stream by GLUT2, a facilitative hexose carrier present in the basolateral membrane. Recent observations suggest that GLUT2 is also present in the apical membrane, however, and may participate in the transport of glucose and fructose from the intestinal lumen into the cells.

Although it was generally assumed that fructose is mainly transported across the enterocytes to be released unchanged into the blood stream, recent evidence indicates that it is already metabolized within the enterocyte, at least to some extent. Specific enzymes for fructose degradation [15] are indeed expressed in the enterocytes. Furthermore, the enterocytes express gluconeogenic enzymes and the

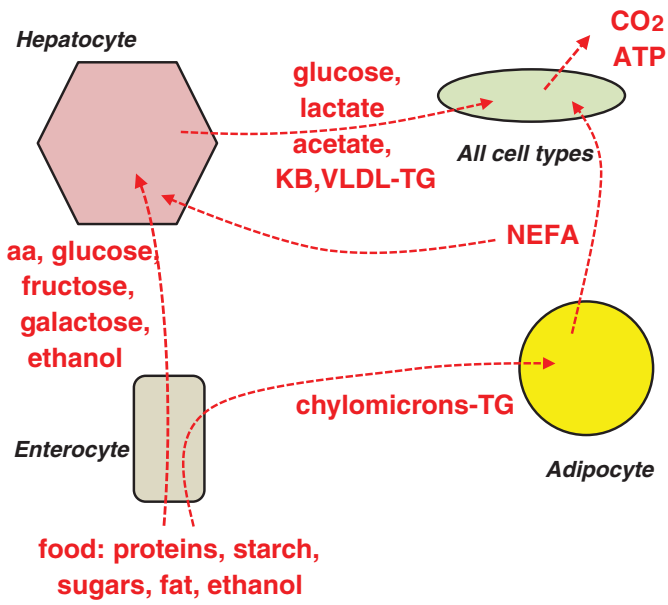

Fig. 31.1 The liver as a metabolic plant. Starch and fat (mainly triglycerides) constitute the major portion of energy intake. Starch is ultimately absorbed as glucose, which is directly absorbed into the blood stream and can be used as an energy substrate by all cells of the organism. Triglycerides are digested and absorbed in the enterocyte as monoglycerides, glycerol, and fatty acids; in the enterocyte, triglycerides are resynthesized and packaged with apoproteins to form chylomicrons; chylomicrons are absorbed in the lympthatic circulation, thus bypassing the liver to reach the systemic circulation. At the level of adipose tissue, chylomicrons-triglycerides are hydrolyzed by the enzyme *lipoprotein lipase* and temporarily stored as triglycerides. When glucose availability is low (between meals), the adipocytes release non-esterified fatty acids (NEFA), which can be used as an energy fuel by most cells (except for neural cells). Amino acids, fructose, galactose, alcohol, and other special energy substrate cannot be directly oxidized as energy substrate by human cells, which, due to their high level of specialization, cannot afford the cost of synthetizing all the enzymes required for the metabolism of any single nutrient. The liver processes such special nutrients into glucose, lactate or acetate, which can then be used by other cell types. In addition, the liver can also preprocess NEFA to shorter water-soluble ketone bodies (KB; aceto-acetate and β-hydroxybutyrate).

enzyme glucose-6-phophatase, and therefore have the ability (otherwise limited to the liver and kidney) to release glucose into the blood stream. By converting some fructose into glucose, the enterocytes may not only process it into a more readily available substrate for extra-hepatic cells, but also increase portal glycemia, and hence activate portal glucose sensors. These sensors may in turn contribute to the satiating effect of meals by signaling the brain to reduce food intake [16, 17]. In addition, enterocytes express specific enzymes allowing the synthesis of lipids from carbohydrate-derived acetyl-CoA, a process called "de novo lipogenesis." There is evidence that, in rodents fed a high-fructose diet for several days, a substantial portion of fructose is converted into triglycerides in the enterocytes, and that these triglycerides are secreted into the lymph, bypass the liver, and are directly released as chylomicrons into the systemic circulation (Fig. 31.2). The functional role(s) of enterocytes in the metabolism of fructose in humans, and its quantitative significance, currently remain unknown [18].

After sucrose ingestion, glucose and the major portion of fructose are released into the portal vein and are therefore delivered to the liver before gaining access to the systemic circulation. Glucose is taken up by hepatocytes through the hexose carrier GLUT2, and is then converted into glucose-6-phosphate by glucokinase an isoform of hexokinase, the synthesis of which is controlled by insulin in the liver.

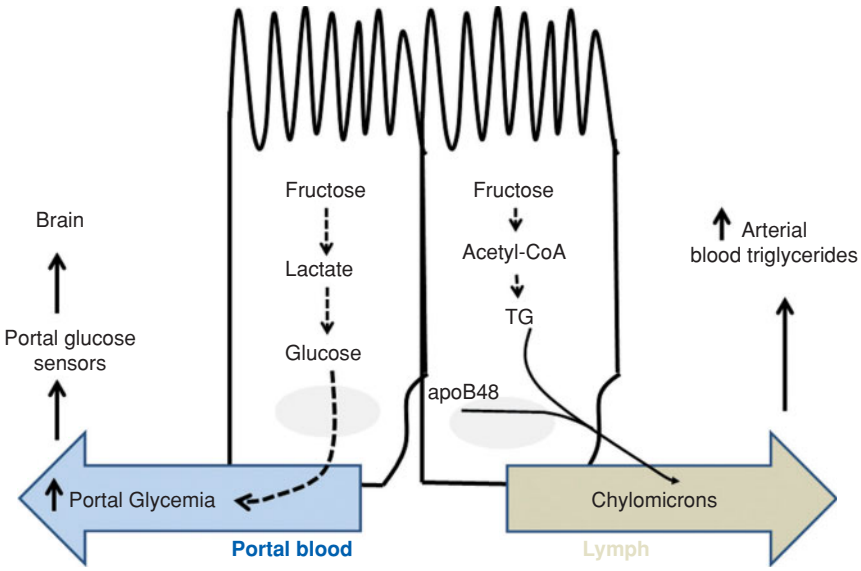

Fig. 31.2 Fructose metabolism in enterocytes. The enterocytes express the key enzymes required to metabolize fructose and convert it into pyruvate and lactate. They also express gluconeogenic enzymes and glucose-6-phophatase, and hence are one of the few cell types (together with hepatocytes and renal cells), which can release glucose into the blood. In rodents, an unspecified portion of fructose is metabolized to lactate and glucose by the gut. In addition to providing glucose as a substrate to other organs, this process may be associated with an activation of glucose sensors in the portal circulation, and play a role in the control of food intake and other metabolic regulations. In addition, enterocytes in the proximal small bowel express the enzymes required for de novo fatty acid synthesis, and may convert part of fructose into triglycerides, package newly formed triglycerides into chylomicrons, and thus contribute to dyslipidemia. Metabolism of fructose in the gut has been demonstrated in rodents but has not been directly assessed in humans. For a color version of this figure, please refer to the color plate.

Glucose-6-phosphate is further metabolized in the glycolytic pathway, in which it is converted into fructose-6-phosphate and trioses-phosphate. Insulin regulates several of the major glycolytic enzymes' activity. One key glycolytic reaction is the conversion of fructose-6-phophate into fructose-1,6 diphosphate. This reaction is controlled by the enzyme phosphofructokinase. The activity of this enzyme is inhibited by ATP and citrate, and hence the overall glycolytic activity is regulated by the energy status of the hepatocyte. As a consequence, only a portion of the portal glucose is metabolized in the liver, and glycolysis is only moderately activated after a glucose meal.

Fructose, as glucose, is transported into the hepatocyte by GLUT2. Once in the hepatocyte, however, its metabolism differs markedly from that of glucose. Fructose is rapidly converted into fructose-1-phosphate by a specific enzyme, fructokinase, and fructose-1-phosphate is then directly converted into triose phosphates (DHAP and glyceraldehyde) by a second enzyme, aldolase B. The Km of fructokinase for fructose is low, and the activity of both fructokinase and aldolase B is high. Furthermore, these two enzymes are not regulated by insulin, ATP, or citrate. As a consequence, portal fructose is nearly completely taken up by liver cells, where it is immediately metabolized to triose phosphates. When fructose intake at a meal is large enough, the triose phosphates generated by hepatic fructose metabolism cannot be directly oxidized and are converted mainly into glucose and lactate, which are released into the systemic circulation to be used as energy fuels by extra-hepatic cells. In addition, hepatic glycogen synthesis is stimulated [19]. When fructose intake is too high, these pathways of hepatic fructose disposal may become saturated, and triose phosphates get converted into fatty acids, to be ultimately either stored as intrahepatic lipids, or secreted as VLDL-triglycerides in the circulation (Fig. 31.3).

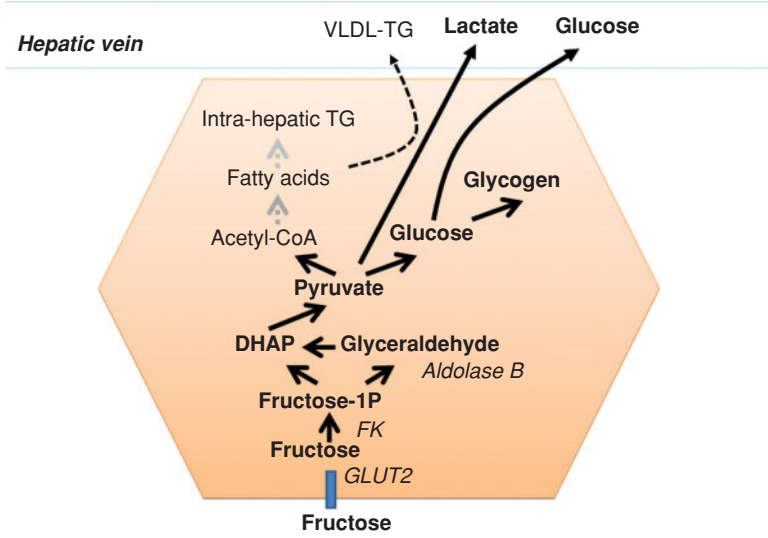

Fig. 31.3 Fructose metabolism in hepatocytes. Fructose is transported into the hepatocyte by the same transporter as glucose, GLUT2. Once inside the cell, it is rapidly converted into fructose-1-phosphate (fructose-1-P) by fructokinase, and then split into dihydroxyacetone-phosphate (DHAP) and phosphoglycerate by aldolase B. These two enzymes are not regulated by insulin; because they are not inhibited by ATP or citrate there is no feedback inhibition of the initial steps of fructose metabolism. DHAP is further metabolized by glycolytic enzymes. However, when a large amount of fructose is ingested, uncontrolled activity of fructokinase (FK) and aldolase B lead to an oversupply of DHAP and glyceraldehyde, and lactate and glucose production are stimulated. Hepatic glycogen synthesis is also stimulated, but this pathway is quantitatively limited. In case of very high fructose intake, fructose conversion into hepatic glycogen, lactate and glucose may become saturated, and hepatic de novo lipogenesis is turned on; this results in an increase of intrahepatic triglycerides (TG) and an enhanced secretion of very-low-density lipoproteins (VLDL). For a color version of this figure, please refer to the color plate.

In subjects receiving high amounts of fructose intravenously during total parenteral nutrition, the rapid conversion of fructose to fructose-1-phosphate has been associated with an ATP depletion and an increase in inorganic phosphate concentration in liver cells, resulting in acute liver dysfunction [20]. This ATP depletion also stimulated uric acid production. It is generally admitted that a high-fructose consumption will stimulate uric acid concentrations, but it has not yet been demonstrated that such ATP depletion occurs after the oral intake of fructose.

It is noteworthy that the liver has evolved different ways to handle fructose and alcohol as energy substrates. Both are dispensable, energy rich substrates that can contribute to the energy needs of humans. For fructose, the enzymatic machinery present in liver cells is highly efficient and results in a nearly complete extraction and breakdown of even large doses of fructose. Many of the potentially deleterious effects of fructose are related to this uncontrolled metabolism, leading to an overflow of triose phosphates in liver cells. In contrast, the metabolism of alcohol through alcohol dehydrogenase is relatively slow, quantitatively limited, and proceeds with first-order kinetics, meaning that it is not stimulated when blood alcohol concentrations increase [21]. As a consequence, the ingestion of even large amounts of alcohol does not impose an overload of energy metabolites upon liver cells, but instead generates small amounts of highly toxic alcohol metabolites in the liver and causes long-lasting increase in blood alcohol, which then causes acute brain intoxication [21].

In addition to the amount of fructose ingested with a meal, several factors modulate fructose metabolism. The chronic consumption of a high-fructose diet increases the absorptive capacity of the gut for fructose, and may accelerate hepatic fructose metabolism by increasing the expression of key metabolic enzymes [22]. Of special concern,

it enhances the conversion of fructose carbons into lipids [23]. In contrast, when fructose is administered immediately before or during exercise, fructose carbons are made rapidly available to the exercising muscle, mainly as lactate [24], and hepatic storage of fructose carbons is minimal.

There remain several open questions regarding fructose metabolism however. GLUT5, the "specific" glucose transporter expressed in the gut and in liver cells, is also expressed in other cell types in the body, including the brain [25]. There exist other, more recently identified "fructose transporters" (GLUT9, SLC2A9), which are expressed in extra-hepatic tissues. Extra-hepatic tissues also synthesize an isoform of fructokinase, ketohexokinase A [15]; although it has a much lower affinity for fructose than the hepatic isoform, it nonetheless suggests that extra-hepatic tissues may metabolize fructose to some extent. Animal or *in vitro* experiments indeed report that fructose can have direct actions on the brain and adipose tissue [26, 27]. However, these effects are observed at high-fructose concentrations, whereas *in vivo* arterial fructose concentrations remain low (in the 50–500 μmol/L range compared to 5–10 mmol/L for glucose), even after ingestion of large fructose doses. Whether some fructose is indeed directly metabolized by extra-hepatic tissues *in vivo*, and what the functional significance of extra-hepatic fructose metabolism may be, presently remains unknown.

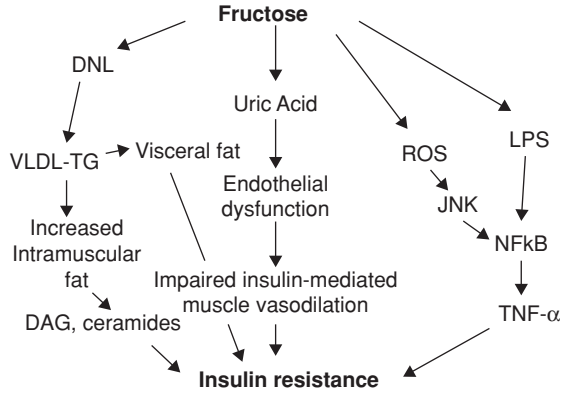

Fig. 31.4 Mechanisms of muscle insulin resistance in rodents fed ahigh fructose diet. (1) A chronic high fructose feeding stimulates hepatic de novo lipogenesis (DNL), resulting in an increase in very-low-density-lipoprotein-triglyceride concentrations in the blood; this secondarily enhances the deposition of fat in visceral adipose tissue and in skeletal muscle fibers. In muscle, accumulation of lipid metabolistes, such as diacyl-glycerols (DAG) and ceramides impair insulin signaling. (2) Fructose increases blood uric acid concentrations, which causes en endothelial dysfunction and impairs insulin-mediated muscle vasodilation, thus decreasing the delivery of both insulin and glucose to skeletal muscle. (3) In the liver, fructose metabolism increases the production of reactive oxygen species (ROS), which triggers inflammation and increases TNF-alpha secretion. NF-kappa B in turn causes whole body insulin resistance. (4) Chronic fructose intake impairs the gut barrier function, causing absorption of bacteria and microbial products in the portal circulation. Bacterial lipopolysaccharides (LPS) triggers inflammation and the secretion of TNF-alpha and other pro-inflammatory cytokines, which contribute to insulin resistance.

31.4 METABOLIC EFECTS OF HIGH FRUCTOSE DIETS IN ANIMAL MODELS

In rodents, high-sucrose or high-fructose diets have been extensively been used as a model for diet-induced obesity and diabetes mellitus. Addition of sucrose to rats' diet or drinking water leads to an increased energy intake and causes excess body weight gain, together with increased total and visceral (epididymal/perirenal) fat mass. While becoming obese, high fructose-fed rats may develop insulin resistance, impaired glucose tolerance, or overt diabetes mellitus, dyslipidemia, hepatic steatosis, hyperuricemia, and high blood pressure.

The mechanisms underlying the development of insulin resistance in fructose-fed animals appear multifactorial (Fig. 31.4): High-fructose fed rats display an important accumulation of "ectopic" fat depots within hepatocytes, skeletal muscle fibers, pancreatic exocrine and endocrine cells, and others. In the liver and in skeletal muscle, these ectopic fat depots are associated with increased concentrations of di-acylglycerols and ceramides, causing "lipotoxicity" and insulin resistance [28]. In addition, fructose metabolism increases the production of reactive oxygen species, and triggers endoplasmic reticulum stress, which impairs insulin signaling [29]. Finally, a high-fructose diet increases blood uric acid concentration. Hyperuricemia in turn impairs endothelial

cell function and insulin-mediated vasodilation, thus contributing to both insulin resistance and high blood pressure [30].

Most rodent studies compare obese, high-fructose fed animals to chow-fed, control rats and therefore do not allow differentiating the effects of fructose as a substrate from those of excess energy intake or obesity. However, one recent study, in which rats were given a slightly hypocaloric, high-fructose diet, suggests that many of these effects may indeed be secondary to exposure to fructose independently of excess energy intake [31].

31.5 EFFECTS OF FRUCOSE ON HUMAN HEALTH

In the United States, it is estimated, based on nationwide nutritional surveys, that the consumption of added sugar represents on average 20% of total energy intake [32, 33]. Given that added sugars contain approximately 50% fructose, this indicates that 10% of total energy is obtained from fructose on average. There is considerable inter-individual variation, however, and about 10% of the US population has fructose consumption higher than 20% total energy. Similar figures have been reported for several European countries [34, 35].

Several small-scale studies have been performed to evaluate the short- to medium-term effects of high-fructose diets in humans. Several of these studies were performed in the 1980s and 1990s, when pure fructose was evaluated as a potential sweetener for type 2 diabetic patients. These studies were primarily designed to evaluate the effects of substituting pure fructose to sugar or starch. Although these studies provide very important pathophysiological information, they may not be directly relevant to real nutrition, where fructose is mainly ingested as sucrose or high-fructose corn syrup, and therefore with nearly equimolar ingestion of glucose.

Several epidemiological studies have also assessed the relationships between fructose and metabolic diseases using large transversal and cohort studies in which detailed nutritional evaluations were included. Because the nutritional databases used for these studies did usually not allow computing fructose intake, they often search for associations of diseases with added sugar intake, or with the consumption of sweetened beverages, which represent approximately one-third to one-half total fructose intake. We will refer to these all these studies having assessed the associations between fructose and diseases.

31.6 FRUCTOSE AND HUMAN OBESITY

Many epidemiological reports indicate that the consumption of added sugar or of sugar-sweetened beverages is positively associated to a high total energy intake and to obesity. Prospective cohort studies further document that it is associated with body weight gain, suggesting that fructose may be one significant factor in the development of obesity. This is however not evidence that fructose, more than any other nutrient consumed in excess, is directly responsible for obesity. Considering that obesity is the result of a long-term mismatch between energy intake and expenditure, this would imply that fructose consumption would either decrease energy expenditure or increase energy intake [36, 37].

Actually, acute oral fructose administration is associated with an increase in postprandial energy expenditure compared to oral glucose [38]. This larger thermic effect is observed in obese and type 2 diabetic subjects as well as in non-obese healthy subjects [39]. Furthermore, short-term fructose overfeeding did not cause major changes in basal or post-prandial energy expenditure, which may account for major weight gain [40–42]. Several studies indicate that the spontaneous food energy intake during a meal is decreased when a sugary drink has been consumed some two hours before. Furthermore, the reduction in food intake is of even larger magnitude that after a glucose drink, suggesting that fructose is more satiating [43]. However, these short-term measurements of spontaneous food intake are known to be relatively inaccurate. In contrast, when glucose or fructose drinks are ingested simultaneously with meals, the post-prandial rise in blood concentrations of leptin and insulin, two hormones that suppress food intake, were significantly lower with the fructose drink as compared to the glucose drink. Furthermore, blood concentrations of ghrelin, a hormone that stimulates food intake, are less blunted with the fructose drink [44]. This may indicate that fructose has a

lower satiating effect than other carbohydrates. These hormones are only three out of several complex factors regulating food intake, however. Therefore, the effect of fructose on food intake in humans remains unclear.

It has also been reported recently that supplemental fructose or glucose drinks, when administered to overweight and obese subjects, led to a similar increase in total body weight. However, an increase of visceral fat mass was observed only with fructose. This suggests that fructose may favor the development of cardiovascular and metabolic diseases by specifically promoting the development of central, abdominal obesity [45]. This effect was observed in males only and needs to be confirmed in a larger sample.

31.7 EFFECT OF FRUCTOSE ON BLOOD LIPIDS IN HUMANS

Soon after fructose was proposed as an alternative sweetener to sucrose for diabetic patients, it was observed that it was associated with hypertriglyceridemia. Since then, numerous studies have reported that consumption of fructose or sucrose can increase fasting and post-prandial triglyceride concentrations in diabetic and non-diabetic subjects [46]. This effect is observed with large daily fructose intakes. Two distinct mechanisms account for this rise of blood triglycerides. First, fructose is a highly lipogenic substrate and some fructose can be converted into lipids by de novo lipogenesis in the liver [47]. Furthermore, de novo lipogenesis can be stimulated several-fold within a few days of exposure to a high-fructose diet [23]. Second, the post-prandial clearance of blood triglycerides is lower after ingestion of a mixed meal containing fructose than after the same meal containing glucose; this may be due to lower blood insulin concentrations with fructose, leading to a lesser stimulation of the enzyme lipoprotein lipase in adipose tissue [48].

Whatever the mechanisms, this effect of fructose may have adverse effects in the long term, because hypertriglyceridemia constitutes an independent cardiovascular risk factor. Furthermore, fructose consumption is associated with an increased proportion of small, dense atherogenic LDL particles, and may further enhance the risk of developing cardiovascular diseases [49].

31.8 FRUCTOSE AND NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent condition in many countries. It can evolve from a mere hepatic steatosis to steatosis associated with inflammation and focal areas of necrosis (nonalcoholic steatohepatitis), to hepatic fibrosis, and eventually to nonalcoholic cirrhosis. In rare cases, it can even proceed to hepatocarcinoma. In addition, the accumulation of fat in the liver is closely associated with insulin resistance. As a matter of fact, insulin resistance and dyslipidemia have been proposed to be more directly related to intrahepatic lipid accumulation than intravisceral fat [50].

Obesity is the leading cause of NAFLD, most likely due to a high rate of non-esterified fatty acid release from adipose tissue, leading to triglyceride synthesis in the liver [51]. Dietary factors are likely to be involved as well. It was observed, in a small sample of NAFLD patients, that intrahepatic fat content is positively correlated with dietary sugar [52]. Genetic factors appear to be involved as well: in the United States, obese Hispanics show a higher prevalence of NAFLD than Caucasians with similar amounts of body fat [53]. Large population studies indicate that a common polymorphism of PNPLA3 (a lipase expressed in hepatic and extrahepatic tissues, which may act both as a lipolytic and lipogenic enzyme [54]) is associated with hepatic fat content [55]. Interestingly, overexpression of PNPLA3 increases de novo lipogenesis and deposition of newly formed lipids in the liver [56]. Moreover, in a multi-ethnic US adolescent population, dietary fructose intake is associated with intra-hepatic fat only in subjects expressing the PNPLA3 variant [57], indicating that genetic factors may modulate the effects of diet.

Based on these observations, dietary fructose is currently suspected to play a significant role in the development of NAFLD. In rodents, adding sucrose to the drinking water rapidly increases intrahepatic fat content before a significant weight gain or whole body insulin resistance develops [28]. In healthy humans, intrahepatic fat content can be increased

twofold after only a few days on a high-fructose, hypercaloric diet [42]. It is suspected that fructose conversion into fat may be responsible for hepatic fat deposition, but the relative contributions of non-esterified fatty acid released from adipose tissue and of fatty acids from hepatic de novo lipogenesis have not yet been documented [58].

The evidence for a causal link between fructose intake and NAFLD in humans remains weak, however. Indeed, a significant increase in intrahepatic fat content was observed in humans during short-term fructose overfeeding experiments, but similar results were also observed with fat or glucose overfeeding. Furthermore, the hepatic fat content observed in healthy individuals (about 2%) remains much lower than the cut-off value used for the diagnosis of NAFLD (>5%) The effects of longer-time fructose administration remain unknown, however.

Although the role of fructose in NAFLD remains hypothetical, there are nonetheless reasons for concern. First, the pathogenic effects of fructose may be restricted to specific subgroups in the population. Second, animal experiments indicate that fructose produces an oxidative stress on liver cells, which in turn may trigger the development of hepatic inflammation and fibrosis. In addition, fructose metabolism leads to the formation of an aldehyde byproduct, methyglyoxal, which may also promote tissue fibrosis [59]. It can therefore by hypothesized that, in the long term, fructose may not only contribute to intrahepatic fat accumulation, but also trigger the switch from benign hepatic steatosis to a more aggressive nonalcoholic steatohepatitis.

31.9 EFFECTS OF FRUCTOSE ON INSULIN SENSITIVITY AND GLUCOSE HOMEOSTASIS

Alterations of blood glucose homeostasis and insulin resistance are prominent features in fructose-fed rodents and non-human primates [60], but are observed only after animals have gained a substantial amount of body fat. The effects of fructose on glucose homeostasis in humans remain much less clearly documented, however. Acute intravenous fructose administration impairs the suppression of hepatic glucose production by insulin [61]. In addition, overfeeding with fructose increases basal hepatic glucose production and impairs its suppression by insulin within a few days [23]. These effects are observed with high amounts of fructose (corresponding to approximately 20–30% total energy intake), however, and are not associated with clinically significant increases in fasting glycemia. Fructose overfeeding is also associated with a modest rise in the glycemic response to an oral glucose load [45], which may be a consequence of impaired hepatic glucose production. However, few studies included a direct measurement of whole body insulin sensitivity with the gold standard method, the hyperinsulinemic euglycemic clamp. Such studies failed to document any muscle insulin resistance (as evaluated by whole body glucose disposal at high insulinemia) in response to fructose [23, 42, 62]. Altogether, there is solid evidence that, in the short term, fructose causes some degree of hepatic insulin resistance, without significantly affecting muscle insulin sensitivity. However, in all these studies, fructose was administered over short periods of time and was not associated with clinically significant body fat gain. As for NAFLD, there is nonetheless a real concern that fructose may significantly impair glucose metabolism when administered over more extended periods of time.

31.10 EFFECTS OF FRUCTOSE ON BLOOD PRESSURE AND URIC ACID CONCENTRATIONS

In some animal studies, high fructose intake has been reported to cause an increase in blood pressure [63]. Hyperuricemia is also frequently reported in high-fructose fed animals, and it is often proposed that this is a direct consequence of an increase in uric acid production [64]. According to this hypothesis, administration of high doses of fructose leads to a rapid hydrolysis of ATP to allow fructose conversion into fructose-1-phosphate in the liver. This causes an intrahepatic depletion of ATP, together with an increase in AMP production and its degradation to uric acid. Recently, it has been further suggested that fructose-induced hyperuricemia may be directly responsible for an increase in blood pressure by impairing endothelium-mediated vasodilation [64].

Whether fructose, ingested with usual foods and beverages, actually causes a similar increase in uric acid concentration remains an area of debate. Some studies documented that uric acid concentrations increased to after acute fructose ingestion or upon chronic fructose intake [65]. The increase is generally of small magnitude, however. The effects of high-fructose consumption on blood pressure in humans also remain controversial. Although most studies do not document an increase in blood pressure in response to fructose, one recent study reported that consumption of a fructose-supplemented diet increased both blood pressure and uric acid concentration. Furthermore, prevention of hyperuricemia by the administration of a uricosuric agent also prevented the rise in blood pressure [66].

31.11 EFFECTS OF FRUCTOSE ACCORDING TO GENDER

In rat studies, the effects of fructose on blood glucose homeostasis are markedly attenuated in females compared with males. However, oophorectomy abolishes these differences, suggesting that sex hormones modulate fructose's effects [67]. In non-obese humans, short-term fructose overfeeding increases fasting plasma triglyceride to a lesser extent in premenopausal women than in men [68]. Premenopausal females also appear to be protected against the decrease in hepatic insulin resistance induced by short-term fructose [69]. Furthermore, a high-fructose diet, when administered over a ten-week period, increases visceral fat mass and enhances the blood glucose responses to a glucose load only in men [45]. These gender effects have not yet received as much attention as needed.

31.12 CONCLUSION

Based on experiments performed in animals, and on short-term studies performed in humans, there is little doubt that a high fructose intake can alter plasma lipid profiles and cause some degree of hepatic insulin resistance. In the long term, it can be suspected that it may also cause extrahepatic insulin resistance and nonalcoholic fatty liver diseases. These effects are documented only with very large amounts of fructose that are usually associated with an energy intake in excess of actual requirements. Whether smaller amounts of fructose may also exert potentially deleterious effects in the long term remains to be evaluated.

Epidemiological studies show that sugar or sweetened beverage intake is positively correlated with heart diseases, dyslipidemia, diabetes, high blood pressure, and hyperuricemia. These relationships are no longer present when body weight is taken into account, suggesting that the effects of fructose are largely mediated by an increase in body fat mass. Further studies are needed to unravel the mechanisms by which fructose may cause obesity. Fructose may promote an excessive energy intake because it may not elicit appropriate satiety signals. Alternatively, it may favor overeating just because it is sweet and that sugar-containing foods (and those containing fat as well) are highly palatable and widely available. It has also been suggested that sugar may be addictive to some subjects. Finally, it is possible that deleterious effects require a long exposure to fructose, and/or are restricted to particular subgroups of subjects.

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