Metabolic Effects of Fructose and the Worldwide Increase in Obesity

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Tappy L, Lê K-A. Metabolic Effects of Fructose and the Worldwide Increase in Obesity. *Physiol Rev* 90: 23–46, 2010; doi:10.1152/physrev.00019.2009.—While virtually absent in our diet a few hundred years ago, fructose has now become a major constituent of our modern diet. Our main sources of fructose are sucrose from beet or cane, high fructose corn syrup, fruits, and honey. Fructose has the same chemical formula as glucose ($C_6H_{12}O_6$), but its metabolism differs markedly from that of glucose due to its almost complete hepatic extraction and rapid hepatic conversion into glucose, glycogen, lactate, and fat. Fructose was initially thought to be advisable for patients with diabetes due to its low glycemic index. However, chronically high consumption of fructose in rodents leads to hepatic and extrahepatic insulin resistance, obesity, type 2 diabetes mellitus, and high blood pressure. The evidence is less compelling in humans, but high fructose intake has indeed been shown to cause dyslipidemia and to impair hepatic insulin sensitivity. Hepatic de novo lipogenesis and lipotoxicity, oxidative stress, and hyperuricemia have all been proposed as mechanisms responsible for these adverse metabolic effects of fructose. Although there is compelling evidence that very high fructose intake can have deleterious metabolic effects in humans as in rodents, the role of fructose in the development of the current epidemic of metabolic disorders remains controversial. Epidemiological studies show growing evidence that consumption of sweetened beverages (containing either sucrose or a mixture of glucose and fructose) is associated with a high energy intake, increased body weight, and the occurrence of metabolic and cardiovascular disorders. There is, however, no unequivocal evidence that fructose

intake at moderate doses is directly related with adverse metabolic effects. There has also been much concern that consumption of free fructose, as provided in high fructose corn syrup, may cause more adverse effects than consumption of fructose consumed with sucrose. There is, however, no direct evidence for more serious metabolic consequences of high fructose corn syrup versus sucrose consumption.

I. INTRODUCTION

A. General Context

Humans, and many mammals, tend to overfeed themselves when presented with a palatable diet, and this trivial observation outlines the importance of sensorial properties of foods in our nutrition. Amongst the factors that make a food palatable, a sweet taste is highly favored by many. This natural attractiveness toward sweetness, which has been translated in many idiomatic expressions (a sweet life, to keep someone sweet, to sweet-talk someone, . . .), is responsible for a substantial consumption of sugars by modern humans.

Sugars are naturally occurring sweeteners, the most common in our nutrition being sucrose, fructose, and glucose. Fructose and glucose are monosaccharides present in small amounts in fruits and honey, while sucrose, a disaccharide formed by one molecule of glucose linked to one molecule of fructose through an α 1–4 glycoside bond, is found in substantial amounts in sugar cane and beets.

Given the substantial participation of fructose in our everyday diet, it appears important to delineate its consequences and metabolic effects. This review therefore focuses on the metabolic effects of dietary fructose and its possible consequences on health. Data collected specifically in humans are addressed, but some studies done on animals are discussed when relevant. Caution should be however called upon their relevance to humans given the very high fructose intake used in many animal studies.

B. Historical Perspective

1. Evolution of fructose consumption through history

Humans have not always been the high sugar-consumers that we are today. Man's ancestors, the Cro-Magnon men during the Paleolithic, obtained their food from hunting and gathering, and their diet was mainly composed of meat. Their nutritional intake was high in protein, moderate in fat, and low in carbohydrates (63). At this time, fruit and berries represented the major source of carbohydrate, while starch consumption was low. It can be speculated that man's natural taste attraction for sweetness dates from these ages, when sugar was scarce.

Honey was the main sweetener, used in limited amounts, until the Crusades, during which time western Europeans got acquainted with sugar used in the Middle East. Consumption of sugars remained however quite low until the 18th century, when both the development of intercontinental trade with distant countries where sugar cane abounded and technological improvement to extract and refine sugars became available. Sugar was no longer a luxury product and quickly became extremely popular. It was initially mostly extracted and refined from cane and imported to Europe and North America, and later was also prepared from beets. Sugar was first consumed as a sweetener in tea and coffee, the new fashionable drinks, but its use was rapidly extended to be preparation of new tasty and palatable food items such as bakeries and sweets. In England, sugar consumption increased by 1,500% between the 18th and 19th centuries (127), and by the turn of the 20th century, sugars had become one major constituent of our diet.

Sucrose remained the almost exclusive sweetener to be consumed, with only small amounts of glucose and fructose ingested essentially with fruits, until the 1960s when the food industry developed and put into use technologies allowing to extract starch from corn, hydrolyze it to glucose, and convert part of the glucose into fructose through enzymatic isomerization (136). This resulted in the production of corn-derived sweeteners, among which was high fructose corn syrup (HFCS) (90, 241). The high sweetening power of HFCS, its organoleptic properties, its ability to confer a long shelf-life and to maintain a long-lasting moisterization in industrial bakeries, together with its low cost, contributed to a very rapid increase in its consumption at the expense of sucrose. HFCS can be produced with various fructose-to-glucose ratios, with the most commonly used being HFCS-55, containing 55% fructose and 45% glucose, i.e., a fructose-to-glucose ratio close to the 1:1 ratio found in sucrose.

C. Fructose Consumption

1. Methods for assessing fructose consumption

Assessing the fructose intake in a population is not an easy task, since fructose intake is not specifically recorded as a variable in most surveys or databases. The two commonly used methods are "per capita disappearance data" and "individual food intake reports."

Per capita disappearance data in the United States have been reported on a yearly basis since 1909. Sweetener disappearance data are available for sucrose, HFCS, and honey. They include both individual consumption and

industrial use for food processing and may thus overestimate real fructose intake due to losses and waste at the consumer level. They nonetheless provide useful estimates of trends in added sugar consumption (http://www.ers.usda.gov/briefing/sugar/data.htm).

Individual food intake records are usually performed over a 1- to 3-day period. By combining the recorded intake of specific foods with their fructose content, it is possible to estimate the individual fructose consumption. This method provides a more accurate view of the fructose intake at the individual level, but extrapolation to whole populations is dependent on population sample selection (163).

2. *Fructose intake between 1970 and 2007 in the United States*

According to United States Department of Agriculture (USDA) reports, per capita added sugar consumption amounted to ~90 g/day in 1970 (225). By this time, HFCS consumption was close to zero. Important changes occurred between 1970 and 1985, when sucrose disappearance progressively declined by almost 50% (Fig. *1A*). This decrease in sucrose consumption was mirrored by a sharp

A Sucrose and HFCS consumption in the U.S.

B Average daily per capita calories from the U.S. food availability

FIG. 1. Evolution of the consumption of high-fructose corn syrup (HFCS) and sucrose in the United States between 1970 and present. HFCS has increased rapidly to replace 50% of the sucrose consumption. Over this period, not only total sugar consumption but also total calorie intake and total fat intake have increased significantly. Source: USDA (http://www.ers.usda.gov).

increase in HFCS disappearance. In 2007, sucrose represented 45% and HFCS 41% of the total added sweeteners disappearance, the remaining 14% being accounted for by glucose syrup, pure glucose, and honey. Per capita disappearance of total caloric sweeteners increased by 15% between 1970 and 2007 (http://www.ers.usda.gov/briefing/sugar/data.htm).

Analysis by Park et al. (163) of food dietary records obtained in 1977–78 in the USDA Nationwide Food Consumption Survey reported that the average daily fructose intake was 37 g in the United States population. This dietary survey also provided useful information regarding the sources of fructose intake and the differences by age classes and by gender. Sugar-sweetened nonalcoholic beverages, such as soft drinks, appeared as the major source of fructose for all classes of age considered, except for children younger than 6 yr and adults older than 50 yr. The highest consumers were adolescents and young adults (19–22 yr) of both sexes. The third National Health and Nutrition Examination Survey, performed in 1988–94 (NHANES III), allows assessment of the evolution of fructose intake between 1977 and the 1990s. Average daily fructose intake in NHANES III was 54.7 g, corresponding to a 46% increase over a 10- to 16-yr period. Males tended to consume higher absolute amounts of fructose than females, but the difference was not significant when intakes were reported as a percentage of total energy intake. Adolescents and young adults remained the highest fructose consumers, and people with the lowest income consumed more fructose than those with the highest incomes. Soft drinks were the main source of fructose intake for any class of age considered, including this time young children and older adults.

A recent reappraisal of these estimates, based on data collected from the NHANES 1999–2004 study, estimated an average fructose intake of 49 g/day. It also documented that HFCS consumption had continuously increased over the past three decades and accounted for 42% of total caloric sweetener consumption in 1999–2004 versus 16% in 1977–1978. Interestingly, this analysis also documented that total energy intake increased by 18% and total carbohydrate intake by 41% during the same period, while contribution of fructose to carbohydrate intake remained nearly constant (135).

On the basis of both per capita disappearance analysis and individual food records analysis, there is no doubt that fructose consumption has increased over the past four decades in the United States, that teenagers and young adults are the highest consumers, and that the sweetened beverages are the main dietary source of fructose. However, a few points should be considered.

Free fructose consumption dramatically increased between 1970 and 2007, as illustrated by impressive exponential curves (33). However, this rise was merely due to the increased use of HFCS, in which fructose is under
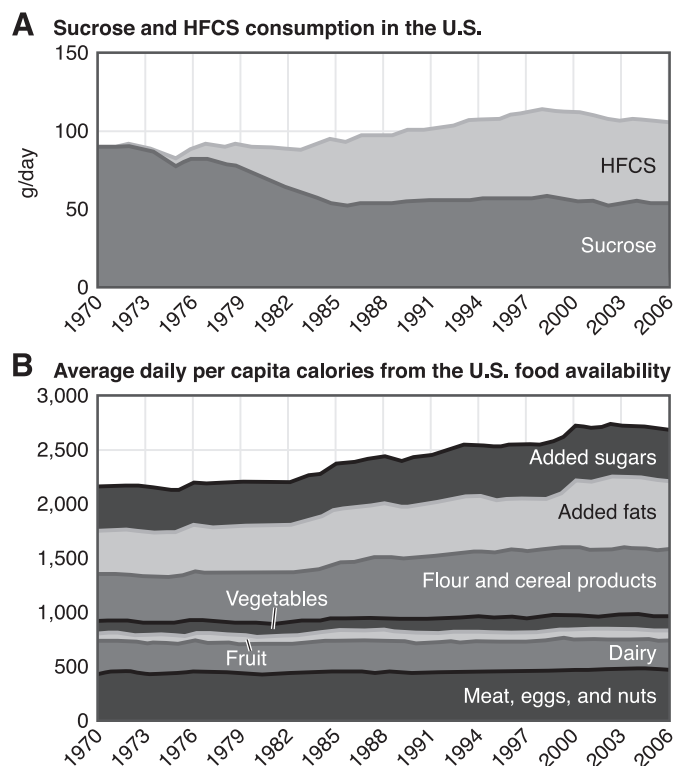
its free form, and was mirrored by a decrease in the consumption of fructose bound to glucose in sucrose. Since there is presently no evidence that the metabolic effects of HFCS-55 (the most widely consumed form of HFCS, containing 55% fructose) differ from those of sucrose (see sect. IV), one should rather consider total fructose, i.e., free plus bound to glucose in sucrose, consumption to assess the nutritional and metabolic impact of fructose.

Over the past decades, there was a general trend toward an increased total energy intake, with all types of foods confounded. From the USDA data (225), total energy intake may have increased by 24%. This includes of course the 15% increase in added sugars discussed above. However, most other nutrients showed the same pattern: fruit consumption also increased by 29%, flour and cereals products increased by 42%, and there was a sharp 55% increase in added fat consumption. Relative proportion of these products remained however comparable (http://www.ers.usda.gov/) (Fig. 1*B*).

3. Fructose intake worldwide

In other parts of the world, data are scarcer than in the United States. The only official source available is the International Sugar Organization, which reports yearly worldwide statistics (104a). Overall, the world average per capita sugar consumption has increased by 16% over the past 20 years, from 56 g/day in 1986 to 65 g/day in 2007. South America and Oceania are the highest sugar consumers, followed by Europe, while low sugar consumption is recorded for Asia and Africa. Sugar consumption recently increased in all part of the world except Oceania, and the most impressive rise was observed in Asia, with a 50% increase (Table 1).

TABLE 1. *World per capita consumption of sugar*

Continent	Per Capita Consumption of Sugar, g/day	
	1986	2006
Europe	107	124
North America*	83	88
South America	117	143
Asia	30	45
Africa	40	46
Oceania	122	118

Values do not include high fructose corn syrup (HFCS). *Lower values compared with Europe are essentially accounted for by a high consumption of HFCS: 1985, 40 g/day; 2005, 52.4 g/day (http://www.corn.org/percaphfcs.htm). [From the *ISO Sugar Year Book*, 2008 (104a).]

II. FRUCTOSE METABOLISM

A. Fructose Absorption and Metabolism in the Gut

Fructose is a hexose, with a chemical formula $C_6H_{12}O_6$ identical to that of glucose. It differs from glucose by the presence of a keto group in position 2 of its carbon chain, versus an aldehyde group at position 1 of the glucose carbon chain. In solution, it can be present as α- or β-pyranoside and furanoside rings.

Fructose present in the gut, whether issued from ingestion of pure fructose or of HFCS, or from the digestion of sucrose at the brush-border membrane, is transported into the enterocyte through a specific fructose transporter, GLUT5, located at the apical pole of the enterocyte. Contrary to glucose, this process does not require ATP hydrolysis and is independent of sodium absorption. Once inside the enterocyte, fructose diffuses into the blood vessels through a transport mediated by GLUT2 at the basolateral pole of the enterocyte (51, 70).

Compared with glucose, fructose absorption appears to be quantitatively limited. Some individuals may have a low capacity to absorb fructose and develop symptoms of diarrhea and flatulence after fructose loading (116, 172), more particularly when fructose is ingested without glucose (221). In rodents, GLUT5 expression is very low until weaning, but can be stimulated by fructose administration (57). Fructose absorption may also be altered by ageing, since in aged rats, absorption of carbohydrates, including fructose, is decreased (78). Fructose transport is also modulated by noncarbohydrate constituents of the diet. Thus, in rats, a diet high in saturated fatty acids (but not in polyunsaturated fatty acids) enhances intestinal fructose absorption (166).

Once inside the enterocyte, part of the fructose appears to be converted into lactate and released into the portal circulation. This intestinal lactate production appears specific for fructose and was shown, in miniature swine, to account for 12% of the absorbed fructose, versus only 2% with glucose (25). Fructose administration also produced a small rise in intestinal glucose production, suggesting that triose-phosphates were converted into glucose within the enterocyte (25). The presence of glucose-6-phosphatase activity in rodent and human intestine is indeed consistent with a gluconeogenic activity in the gut (170). The functional significance of this intestinal metabolism of fructose remains unknown. It has been suggested that intestinal gluconeogenesis may secondarily exert effects on peripheral metabolism and on food intake through neural reflexes elicited by activation of portal glucose sensors (144).

In the hamster, a high-fructose diet leads to an increase in plasma triglyceride concentrations. These triglycerides, present in the circulation under the form of chylomicrons, were shown to originate from fructose con-

version into fatty acids within the enterocyte (intestinal de novo lipogenesis), with subsequent association with apoB-48 to be released as chylomicrons (88, 126). Whether a similar pathway is active in humans and other mammals remains however unknown.

B. Hepatic Metabolism

After fructose absorption, the fructose present in the portal blood is rapidly and efficiently extracted by the liver (see Fig. 2). Fructose uptake in the liver is thought to be operated by the glucose transporter GLUT2 (43, 49). The bulk of ingested fructose is extracted at first pass in the liver where it is rapidly metabolized into fructose-1-phosphate (P) under the action of the enzyme fructokinase, which is highly specific for fructose. Fructokinase is characterized by a low K_m for fructose [~0.5 mM (2, 93)] and a high V_{max} (estimated at ~3 μmol/min per gram rat or human liver at 25°C) (2, 92)]. These properties account for a rapid metabolism of fructose in liver cells. Inherited deficiency of fructokinase leads to a rare, benign condition called hereditary fructosuria (95). The loss of fruc-

FIG. 2. Fructose metabolism in liver cells. Fructose metabolism (grey arrows) differs from glucose (black arrows) due to *1*) a nearly complete hepatic extraction and *2*) different enzyme and reactions for its initial metabolic steps. Fructose taken up by the liver can be oxidized to CO$_2$ and then converted into lactate and glucose; glucose and lactate are subsequently either released into the circulation for extrahepatic metabolism or converted into hepatic glycogen or fat. The massive uptake and phosphorylation of fructose in the liver can lead to a large degradation of ATP to AMP and uric acid.

tose into the urine in this condition illustrates well the fact that fructose having escaped hepatic metabolism is poorly metabolized in extrahepatic tissues.

Subsequent steps of fructose metabolism have been described in full detail elsewhere (138, 150) and are only briefly outlined here. Fructose-1-P is further metabolized into triose-P through the action of aldolase B. Inherited deficiency of aldolase B is a rare condition leading to hereditary fructose intolerance, characterized by the occurrence of hypoglycemia upon exposure to dietary fructose and by the development of liver steatosis and cirrhosis (95).

The hepatic metabolism of fructose differs markedly from that of glucose for several reasons. First, entry of glucose in the glycolytic pathway is under the control of hexokinase IV, or glucokinase. This enzyme is characterized by a high K_m for glucose, and hence, the rate of glucose phosphorylation varies with changes in portal glucose concentration (105). Glucose-6-P is then converted to fructose-6-P, then to fructose-1,6-di-P through a reaction catalyzed by phosphofructokinase. The activity of phosphofructokinase is inhibited by ATP and citrate, which allows regulation of the reaction according to the energy status of the cell (217). Fructose-1,6-di-P is further converted into pyruvate prior to entry into the Krebs cycle. Altogether, conversion of glucose to pyruvate is regulated by insulin, which stimulates glucokinase gene expression and activates glycolytic enzymes, and by the energy status of the cell. In contrast, fructose conversion to triose-P occurs independently of insulin and is a rapid process due to the low K_m of fructokinase for fructose, and absence of negative feedback by ATP or citrate. This leads to a transient depletion of free phosphate and a decrease in ATP in liver cells in response to fructose (35, 52).

Triose-P produced from fructose can subsequently be converted into pyruvate and oxidized into CO$_2$ and H$_2$O in the tricarboxylic acid cycle. A portion of the triose-P produced is however converted into lactate to be released into the systemic circulation (27). This probably accounts for the significant increase in plasma lactate concentrations observed after fructose ingestion. This fructose-induced lactate production may be quantitatively important during intravenous fructose administration and has occasionally been associated with lactic acidosis (243). The major portion of triose-Ps produced from fructose metabolism is converted into glucose and glycogen through gluconeogenesis (30, 118). Glucose and lactate production may not be entirely independent processes: in rats, it was documented that the main portion of fructose reaching the portal circulation was taken up by periportal hepatocytes, where nearly half of it was converted into glucose, while lactate release occurred essentially in perivenous hepatocytes. This suggested that fructose-induced lactate production results in periportal conversion of fructose into glucose and the subsequent uptake and glycolysis to lactate in perivenous hepatocytes (36).
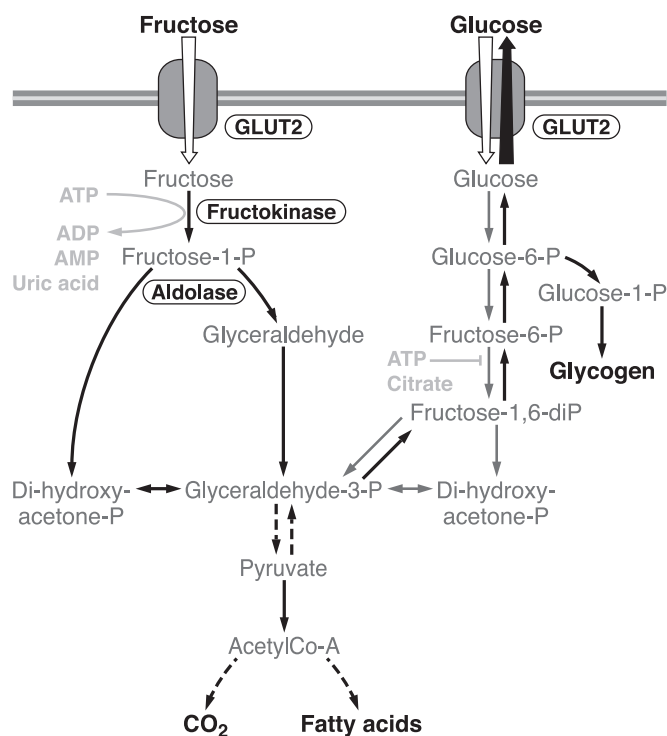
Finally, part of the carbon atoms of fructose can be converted into fatty acids in hepatocytes through the process of de novo lipogenesis. The existence of this pathway was documented by the observation that, in the rat in vivo (17) and in isolated rat hepatocytes (47, 214), administration of [14C]fructose led to 14C incorporation in liver lipids. Stimulation of hepatic de novo lipogenesis can indeed be documented after acute administration of fructose, or of fructose-glucose mixtures, in humans by monitoring incorporation of infused 13C-labeled acetate into very-low-density lipoprotein (VLDL)-palmitate (165, 190). In vitro data indicated that lactate rather than triose-P is the main lipogenic precursor after fructose administration and that activation of pyruvate dehydrogenase by high-fructose diets is a major regulatory step in this process (41, 59, 162). Simultaneously, fructose inhibits hepatic lipid oxidation, thus favoring fatty acid reesterification and VLDL-triglyceride (TG) synthesis (214). Although not specifically measured with fructose, stimulation of de novo lipogenesis by carbohydrate is likely to take place mainly in perivenous hepatocytes, which are characterized by active lipogenic pathways, whereas periportal hepatocytes are mainly oxidative (87).

Another metabolic effect of acute fructose administration is exerted through an increased intrahepatic fructose-1-P concentration. This rise in fructose-1-P has important indirect effects on hepatic glucose metabolism by modulating glucokinase activity. Hepatic glucokinase is a key regulatory enzyme in hepatic glucose metabolism, since it is required for the formation of glucose-6-P. Decreased activity of glucokinase secondary to heterozygous mutations indeed leads to decreased postprandial hepatic glycogen synthesis (232). Glucokinase also acts as a liver sensor for glycemia and is involved in the inhibition of hepatic glucose release by portal hyperglycemia, a process which is also impaired in patients with glucokinase mutations (203). Glucokinase activity is controlled by the concentration of its substrate glucose and by a regulatory protein, which acts as a competitive inhibitor of glucose for glucokinase. Fructose-1-P, at low concentration, antagonizes glucokinase regulatory protein, thus enhancing glucokinase activity (229). As a consequence, addition of small, so-called "catalytic" doses of fructose to a glucose meal can enhance hepatic glucose disposal (69).

C. Extrahepatic Metabolism

After ingestion of fructose, the increase in plasma fructose concentration remains in the micromolar range, indicating that first-pass hepatic extraction is close to 100%. As a consequence, fructose metabolism does not occur in extrahepatic cells to any significant extent under usual conditions. When fructose is administered parenterally, systemic plasma fructose concentrations increase up to 1–2 mM (219). Even under such conditions, extrahepatic fructose metabolism can be expected to be small, since extrahepatic cells do not express fructokinase, and the K_m of hexokinase for fructose is high (138). In this regard, the functional significance of the intestinal fructose transporter GLUT5 being expressed in several extrahepatic tissues including the kidney and adipose tissue remains unknown (50, 129). Catheterization studies showed that, during high-dose fructose infusions, which increased plasma fructose up to 3 mM, kidney fructose uptake accounted for ~20% of total fructose metabolism (27). Such an extrahepatic fructose uptake is however unlikely to occur under physiological conditions.

D. Metabolic Fate of an Oral Fructose Load in Healthy Subjects

After ingestion of a fructose load, plasma glucose and insulin showed little changes, and plasma fructose concentrations rose only to ~50–500 μM (133, 205) (see Fig. 3). There was, however, a rapid and sharp increase in net
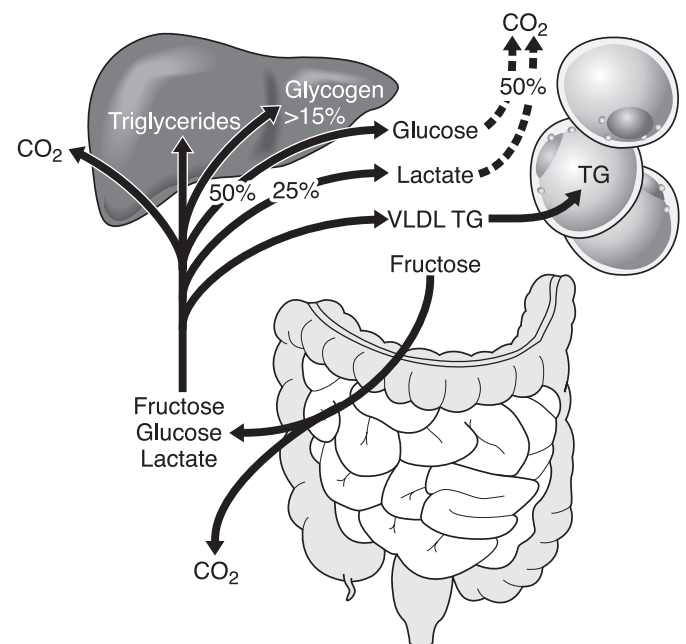
FIG. 3. Metabolic fate of an oral fructose load: after fructose ingestion, fructose metabolism takes place essentially in splanchnic tissues. In the liver, a large proportion of fructose is converted into glucose, which can be either stored as hepatic glycogen or released as plasma glucose. Part of the fructose load is converted into lactate in enterocytes and in the liver, which leads to increased lactacidemia. A small portion of fructose is converted into fatty acids; although quantitatively minor, this pathway may play an important role in the development of fructose-induced hepatic steatosis and dyslipidemia. The estimated contribution of glucose production, glycogen synthesis, lactate production, and total oxidation is indicated based on experimental data described in section IID. Data for lipogenesis and very-low-density lipoprotein (VLDL)-triglyceride (TG) secretion are not available, but these pathways are quantitatively minor.

carbohydrate oxidation (205). Part of this oxidation is likely to take place in the liver. In addition, when ^{13}C-labeled fructose is administered, one can observe that ~50% of the fructose load recirculates as ^{13}C-labeled glucose in the systemic circulation over the next 6 h (62); this indicates that a substantial portion of ingested fructose is converted into glucose in hepatic cells, to be subsequently oxidized in extrahepatic tissues. Catheterization studies, performed in healthy human subjects fasted for 60 h, also indicated that ~50% of infused fructose was released as glucose in the systemic circulation (26). Infusion of ^{13}C-labeled fructose similarly led to an important release of ^{13}C-labeled glucose into the circulation (218, 219), supporting the view that glucose synthesis is the major pathway of hepatic fructose disposal. Interestingly, stimulation of glucose synthesis by fructose does not lead to an increase in total glucose output (219). Acute stimulation of gluconeogenesis by administration not only of fructose, but also of other gluconeogenic precursors such as lactacte (109) or glycerol (106), also fails to increase total glucose output, through a process called autoregulation of glucose production, which involves an inhibition of glycogenolysis (53). It however acutely impairs insulin-induced suppression of glucose production, and hence decreases hepatic insulin sensitivity (67, 189).

A substantial portion of fructose-derived glucose appears to be directly stored as hepatic glycogen. Fructose administration increases even more hepatic glycogen concentrations than administration of an equivalent dose of glucose in both rats (118) and humans (151). In humans, hepatic glycogen synthesis has been shown to account for ~17% of an oral glucose load (167). Although hepatic glycogen synthesis after oral fructose has not been measured in humans, it can therefore be safely estimated to be at least 17%.

Part of the fructose taken up by the liver is also converted into fatty acids through the process of de novo lipogenesis, to be released into the systemic circulation with VLDL. This pathway, although potently stimulated by fructose, represents only a minor portion of the fructose load (46, 141, 165). Finally, there is an increase in plasma lactate, which strongly suggests that hepatic conversion of fructose to lactate, as observed in animals and in humans during intravenous fructose infusion, is one significant pathway for hepatic fructose disposal (36, 207, 219). Catheterization studies indicated that, in healthy fasted subjects, ~25% of ingested glucose was released as lactate from the splanchnic bed during intravenous fructose infusion (26, 66).

One of the effects of fructose administration is a marked suppression of nonesterified fatty acids in the blood, which indicates an inhibition of adipose tissue lipolysis (205). The integrated postprandial inhibition of plasma nonesterified fatty acids was even of comparable magnitude after ingestion of equivalent amounts of glucose or fructose (28). Although very modest compared with what is observed after glucose ingestion, the slight increase in plasma insulin elicited by fructose is sufficient to explain this effect due to the extreme sensitivity of adipose cells to insulin (205). It has also been proposed that fructose-induced hyperlactatemia may contribute to the suppression of adipose lipolysis (1).

Fructose administration, as glucose, increases resting energy expenditure. The thermic effect of fructose is, however, significantly higher that with glucose, and this effect is observed with both fructose alone (205) and with fructose added to a meal (191). This is best explained by the high ATP need linked to fructose-induced gluconeogenesis, with possible contribution of de novo lipogenesis (204). It has been shown that an activation of the sympathetic nervous system plays a role in glucose-induced thermogenesis (185, 239). A role of sympathetic nervous system activation is, however, unlikely to be operative with fructose, since fructose infusion does not activate the sympathetic nervous system (234).

E. Metabolic Fate of an Oral Load of Fructose in Diabetic Patients

The glycemic index of fructose is very low compared with glucose (19 and 100, respectively) (82). This property initially elicited a great interest for the use of fructose as a potential beneficial sweetener in patients with diabetes mellitus. One further characteristic of fructose, which suggested that it was well suited for diabetic patients, is that fructose does not require insulin either for its transport into hepatic cells or for the initial steps of its hepatic metabolism. When administered to diabetic patients, fructose indeed produced minor increases in plasma glucose and insulin concentrations compared with glucose (54, 56). The plasma insulin response to fructose was however markedly enhanced in diabetic patients compared with nondiabetic subjects. The stimulation of carbohydrate oxidation and of gluconeogenesis after fructose ingestion appeared globally similar in healthy nondiabetic subjects and in diabetic patients (161, 196). As in healthy subjects, the enhanced gluconeogenesis induced by fructose appeared to be compensated by an autoregulatory process, involving mirror inhibition of glycogenolysis, so that overall glucose output and glycemia did not change to any great extent (161). Of interest, glucose-induced thermogenesis is frequently blunted in insulin-resistant patients, while fructose-induced thermogenesis remains comparable to that observed in controls (196). This is likely explained by the fact that, in insulin-resistant subjects, intracellular glucose metabolism is decreased, leading to lower glucose-induced thermogenesis, while hepatic fructose metabolism is not impaired.

F. Fructose and Exercise

Physical exercise requires a continuous supply of energy to the working muscle, and muscle contraction increases muscle glucose oxidation by severalfold (94). Glucose oxidized by muscle during exercise originates either from blood glucose through exercise-induced translocation of GLUT4 (242), or from muscle glycogen. Muscle fatigue is a complex phenomenon, still incompletely understood, in which a decrease in glycemia and/or exhaustion of muscle glycogen store can play a major role (9). The development of sport drinks and supplements, aimed at preventing a drop in glycemia during exercise and sparing muscle glycogen oxidation, has therefore been the focus of intense research. In this context, fructose has attracted considerable attention.

Fructose can indeed be metabolized during exercise. When infused intravenously during an exercise of moderate intensity, it was shown that ~80% of the dose of fructose administered was metabolized in splanchnic tissues to be released as glucose, pyruvate, and lactate which were subsequently metabolized in working muscle. The remaining 20% were metabolized directly in working and resting skeletal muscle (5). Due to intravenous rather than oral administration, fructose concentration was however very high (up to 6 mM), and it is unlikely that such direct muscle fructose metabolism occurs with the low plasma fructose concentrations elicited by oral fructose. When oxidation of oral glucose or fructose drinks were compared during an exercise of moderate intensity, it was reported that fructose oxidation was comparable to that of glucose (3), or slightly lower (107), and that fructose conversion into glucose accounted for about half of the total glucose production (107). Thus, even though fructose ingestion per se does not increase plasma glucose concentration, it may nonetheless contribute to maintain glycemia by sustaining glucose production during exercise (107).

Sport drinks aim to prevent a drop of glycemia and to provide exogenous glucose to the working muscles. When oral glucose was administered, exogenous glucose metabolism was however limited to a maximum of ~1.0–1.1 g/min, most likely due to saturation of intestinal glucose transport when higher doses are administered (111). When a mixture of glucose and fructose was administered, total carbohydrate oxidation could however be further enhanced by ~40% (110, 235). This may be explained by the different transport systems used for intestinal absorption of glucose and fructose and by their different metabolism, i.e., essentially hepatic for fructose versus primarily within the skeletal muscle for glucose during exercise. It was also reported that moderate doses of fructose reduced the perception of fatigue and stress during exercise (186) and improved exercise performance during a cycling exercise (58).

Regarding the effects of fructose on muscle glycogen synthesis, few contradictory studies were performed. One study showed that fructose was more efficient than glucose to prevent the decrease in muscle glycogen (assessed from a postexercise muscle biopsy) (125), but another study, using similar techniques, observed no difference between fructose and glucose drinks (117). One study compared muscle glycogen recovery after exercise with glucose and fructose feeding. In this study, muscle glycogen repletion, evaluated with ^{13}C-NMR spectroscopy, was considerably more efficient with glucose than with fructose (227).

On the basis of these studies, the use of fructose as a supplement in sports drinks may possibly have modest advantages, which however remain to be better documented by larger studies in which performance or endurance are the primary outcome. One concern with the use of fructose during exercise is that it may be incompletely absorbed from the gut and get fermented by intestinal bacteria (145), which may limit the amount that can be administered without adverse gastrointestinal symptoms.

G. Fructose and Food Intake

The effects of fructose on appetite remain controversial. While some studies have shown that ingestion of a fructose load alone reduces subsequent food intake (180, 216), this effect was not observed when fructose was ingested together with a mixed meal (181). There are several reasons to suspect that fructose, based on its known physiological effects, will elicit lower satiation than equivalent doses of glucose or complex carbohydrates. First, the postprandial rise in glycemia plays, directly or indirectly, an important role in the mechanisms controlling satiety and food intake. This effect is likely blunted with fructose, since its glycemic index is about fivefold lower than that of glucose. Second, ingestion of fructose-containing meals elicits a lesser suppression of the appetite-stimulating hormone ghrelin and a lower increase in leptin than meals containing an equivalent amount of glucose (207), which suggests that fructose may be less efficient than glucose to suppress food intake. Although acute fructose ingestion is not expected to stimulate leptin secretion, significant increases in fasting leptin concentrations were observed after 1–4 wk of fructose overfeeding (122); this indicates that fructose overfeeding exerted metabolic effects on adipose cells, which may in the long term contribute to suppress food intake. It was also observed that body weight gain was similar in overweight women subjected to a 10-wk supplementation with either glucose or fructose, suggesting that, in the long term, the effects of fructose and glucose on food intake may not differ in a significant way (199).

In addition to producing a lesser secretion of leptin compared with equivalent doses of glucose, it was observed

that a high fructose intake impairs leptin's actions, thus causing a state of leptin resistance. In fructose-fed rats, the anorectic effects of intraperitoneally administered leptin were nearly abolished; this corresponded to a significant decrease in hypothalamic signal transducer and activator of transcription-3 (STAT-3) phosphorylation in response to fructose (193). It was also observed that, in rats, a high-fructose diet caused hepatic leptin resistance through an enhanced amount of suppressor of cytokine 3 and through decreased serine/threonine phosphorylation of key proteins in leptin signaling. At the level of the liver, where leptin promotes fat mobilization and oxidation, this hepatic leptin resistance may contribute to the pathogenesis of fructose-induced nonalcoholic fatty liver disease (NAFLD) (233).

One intriguing observation has been recently reported: it is well known that glucose is the primary fuel for the brain and that changes in glucose concentrations may act as a signal informing the brain about the metabolic and nutritional state of the organism. Accordingly, administration of glucose in the cerebral ventricles suppressed food intake through an increase in ATP-to-AMP ratio and an increased malonyl-CoA content in specialized hypothalamic areas (97). When fructose was infused intracisternally instead of glucose, opposite effects were observed, i.e., a drop in ATP-to-AMP ratio, a stimulation of AMPK activity, lowered malonyl-CoA, and increased food intake (42). The physiological significance of this observation remains however unclear, since plasma fructose concentration will never exceed the micromolar range under physiological conditions, and hence fructose ingestion is unlikely to increase fructose concentration in the cerebrospinal fluid.

III. LONG-TERM EFFECT OF FRUCTOSE

Given the low glycemic rise induced by fructose ingestion, and the fact that its metabolism does not strictly require insulin secretion, several studies evaluated the metabolic effects of replacing part of the carbohydrate intake of patients with type 2 diabetes mellitus with fructose. These studies reported conflicting results, in part explained by variations in experimental conditions (duration of treatment, type of carbohydrate replaced by fructose in the diet, etc.). Only about half of them resulted in a significant reduction in blood glucose (10, 14, 16, 55, 56, 85, 139, 154, 210, 211). These studies however pointed out the fact that fructose was associated with a substantial increase in plasma triglyceride and a decrease in high-density lipoprotein (HDL)-cholesterol.

In animal models, numerous studies have addressed the effects of diets enriched with fructose or sucrose. As a whole, they indicated that high-fructose/high-sucrose diets lead to several adverse metabolic and cardiovascular effects, including dyslipidemia, insulin resistance, hypertension, hyperuricemia, and weight gain (24, 91, 123).

A. Dyslipidemia

It has been long recognized that feeding a high-fructose diet for more than 1 wk increases plasma total- and VLDL-triglycerides in healthy volunteers and in patients with insulin resistance or type 2 diabetes. An increase in total cholesterol was also encountered in some of these studies (14, 55, 133). The mechanisms underlying fructose-induced dyslipidemia have been partially elucidated (see Fig. 4). Plasma triglyceride kinetics were measured in rats fed high-sucrose, -glucose, or -fructose diets: it was observed that, compared with glucose, fructose and sucrose both increased triglyceride production and decreased triglyceride clearance (113). Fructose, by providing large amounts of hepatic triose-phosphate as precursors for fatty acid synthesis, is highly lipogenic. It has indeed been observed in several studies that hepatic de novo synthesis is stimulated after acute fructose ingestion, with fructose contributing to the synthesis of both the glycerol- and the fatty-acyl parts of VLDL-triglycerides (46, 165). Fructose may, in addition, increase the expression of key lipogenic enzymes in the liver. It has been shown to induce the expression of the factor of transcription SREBP-1c, the principal inducer of hepatic lipogenesis (137, 194). Furthermore, this effect was independent of changes in insulin concentrations (137, 147). This effect
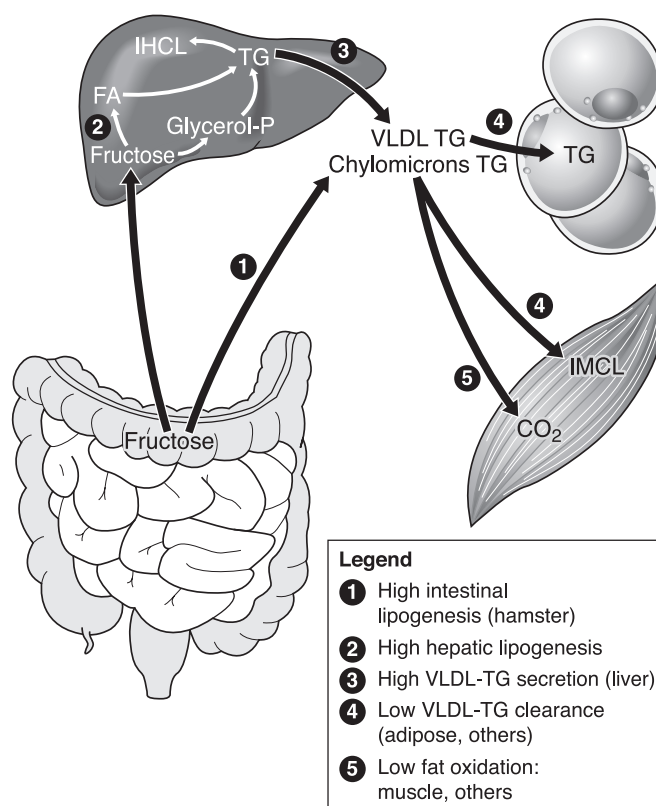

FIG. 4. Possible mechanisms involved in fructose-induced dyslipidemia.

of fructose on SREBP-1c was further shown to require peroxisome proliferator-activated receptor γ coactivator 1β (PCG-1β). Fructose also activates the hepatic transcription factors carbohydrate-responsive element binding protein (ChREBP), which upregulates the expression of hepatic fatty acid synthase and acetyl-CoA carboxylase (64, 118). A high-fructose diet increases the expression of the enzyme glucose-6-phosphate dehydrogenase, the first enzyme in the hexose monophosphate pathway, and intermediary substrates of the hexose-monophosphate shunt have been proposed as being responsible for activation of ChREBP (118, 226).

The role played by a stimulation of hepatic de novo lipogenesis in fructose-induced hypertriglyceridemia is supported by *1*) the positive correlation observed between fractional hepatic de novo lipogenesis and fasting triglycerides in healthy subjects fed an isocaloric, high-sugar diet (100) or a hypercaloric, high-fructose diet (76) and *2*) the fact that a 2-wk supplementation with fish oil reduced both hepatic de novo lipogenesis and fasting triglycerides in healthy subjects overfed with fructose (76). In addition to this increase in fasting plasma triglycerides, acute fructose administration also increased the postprandial rise in plasma triglycerides due to an impaired clearance of triglyceride-rich lipoprotein (46). The same effect was observed with chronic high fructose intake. In overweight women, postprandial triglyceride excursions were enhanced by the consumption of fructose-sweetened beverages over a 10-wk period, indicating that fructose impaired triglyceride clearance (202). This suggests that impaired triglyceride-rich lipoprotein clearance contributes to the hyperlipidemia induced by high-sugar and high-fructose diets (164). This effect of fructose was significantly increased in obese hyperinsulinemic women compared with normal-weight women, suggesting that fructose may produce more severe alterations of lipid homeostasis in insulin-resistant individuals (208). Interestingly, administration of equivalent amounts of pure fructose, sucrose, mixtures of glucose and fructose, or HFCS led to similar increases in postprandial triglyceride; since sucrose, glucose + fructose mixture and HFCS contained approximately half the amount administered with pure glucose, this suggested that coingestion of glucose significantly potentiated the hypertriglyceridemic effect of fructose (198).

Apolipoprotein E is known to be associated with the metabolism of triglyceride-rich lipoproteins. Three common alleles of apoE are encountered in the population: APOE*E2 (E2), APOE*E3 (E3), and APOE*E4 (E4). In population studies, plasma triglycerides are higher in individuals with E2 and E4 alleles (60). It was indeed reported that hypertriglyceridemia was related to sucrose consumption only in individuals with the E2 allele (74). These isolated observations were however not confirmed by an intervention study in which subjects were submitted to an increase in dietary

sucrose intake of 40 g/day: in these subjects, sucrose supplementation failed to alter fasting or postprandial triglycerides, irrespective of the presence or not of the APOE2 allele (75). The possible relationship between apoE polymorphism and the hypertriglyceridemic effect of fructose/sucrose needs therefore to be further documented by larger studies or with higher dietary intakes.

Interestingly, both animal and human studies indicate a gender difference in fructose-induced hypertriglyceridemia: in male rats, chronic high-fructose or high-sucrose diets caused hypertriglyceridemia. In contrast, female rats appeared protected against fructose- or sucrose-induced changes in metabolism (10, 11, 96). This protection was no longer present after oophorectomy, suggesting that female sex hormones may confer protection against the effects of a fructose diet (11). In humans, data are more scarce. Several studies nonetheless reported that the increase in plasma triglyceride induced by fructose feeding was markedly blunted in premenopausal, healthy females compared with age-matched males (12, 15, 198).

The various studies discussed above have addressed the hyperlipidemic effects of fructose, using a large range of dietary fructose/sucrose intake. Since many of the aforementioned studies used a high amount of dietary fructose, the effects of usual fructose intake on plasma triglyceride remain disputed. A meta-analysis (131), compiling the results of all published studies having evaluated the effects of dietary fructose (excluding studies done with HFCS), concluded that a fructose intake >50 g/day (i.e., close to average daily intake in the United States; see sect. II) was associated with increased postprandial triglyceride excursions, while a fructose intake >100 g/day was associated with increased fasting triglycerides.

B. Ectopic Lipid Deposition in the Liver and Skeletal Muscle

In addition to altering plasma lipid profile, fructose may also modulate intracellular lipid deposition (so-called "ectopic lipids," i.e., deposition of triglyceride in the cytoplasm of nonadipose cells, such as hepatocytes, muscle fibers, or endocrine cells; Ref. 224). Such ectopic lipid deposition in the liver and skeletal muscle is closely linked to tissue-specific insulin resistance (224). In rodents, a high-sucrose diet rapidly, within 1 wk, increased intrahepatic fat deposition (159). This effect of fructose may involve both a stimulation of de novo lipogenesis through an enhanced intrahepatic synthesis of triose-phosphate precursors and an increased expression of lipogenic genes (Fig. 5). At the molecular level, it was suggested that mechanisms may involve an inhibition of PPARα in liver cells, a stimulation of hepatic de novo lipogenesis and a reduced hepatic lipid oxidation (183). This deposition of intrahepatic fat in response to fructose

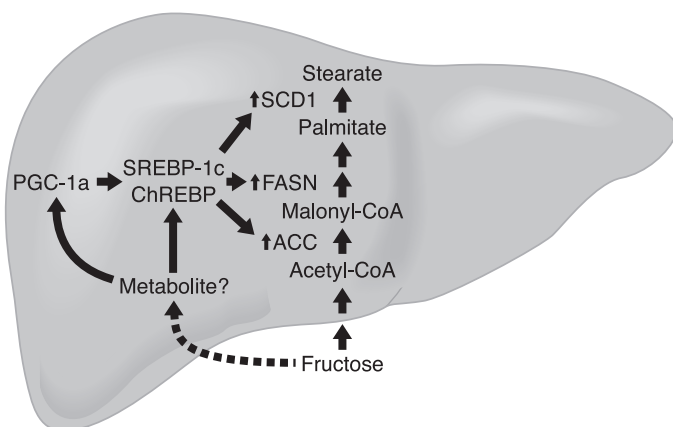## Mechanisms for fructose-induced hepatic de novo lipogenesis

FIG. 5. Mechanisms for fructose-induced de novo lipogenesis: fructose acutely and chronically increases intrahepatic de novo lipogenesis. Stimulation of fatty acid synthesis can be explained by *1*) the unregulated provision of trioses-P and acetyl-CoA secondary and *2*) an increased expression of key lipogenic genes induced by chronically high fructose intakes. A high-fructose diet stimulates SREBP-1c and ChREBP through unknown mechanisms; stimulation of the hexose-monophosphate pathway and increased concentration of metabolites such as xylulose-5-phosphate have been proposed. Coactivation of SREBP-1c by PGC-1β appears to be involved.

was shown to require PGC-1β, which may act as a coactivator of SREBP-1c. Interestingly, inhibition of PGC-1β in rats prevented both hepatic fat deposition and insulin resistance in response to a high-fructose diet (148).

In the early stage of sucrose overfeeding, rodents thus develop significant alterations of hepatic metabolism and of hepatic insulin sensitivity, with relatively little alterations of glucose homeostasis and no significant alterations of extrahepatic insulin sensitivity. However, when the high-sucrose diet is sustained over a few more weeks, accumulation of intramyocellular lipids and muscle insulin resistance develop (159).

In humans, accumulation of intrahepatic fat following fructose ingestion has been less documented. It has been reported that overfeeding healthy male volunteers with 1.5 g·kg fructose body wt^{-1}·day^{-1} (corresponding roughly to the content of 2 liters of standard soda beverages) did not significantly alter fat or muscle liver content (122). However, administration of twice as much fructose over only 7 days induced a significant increase in hepatic and intramyocellular fat content (121). The increase in intrahepatic fat positively correlated with the increase in fasting VLDL-TG, suggesting that these two parameters may be driven by a common mechanism, presumably a stimulation of hepatic de novo lipogenesis. Interestingly, the increase in plasma VLDL-TG in intrahepatic fat content was enhanced in nondiabetic offspring of patients with type 2 diabetes mellitus. This suggests that the metabolic effects of fructose may be dependent on the ge-

netic environment. Given the fact that offspring had a lower insulin sensitivity than subjects without a family history of diabetes, this may also indicate that the dyslipidemic effects of fructose are enhanced by the presence of insulin resistance (121).

C. Impaired Glucose Homeostasis and Insulin Resistance

The relationship between disturbed lipid metabolism and insulin resistance has been recognized since the seminal work of Sir Philip Randle in the 1960s (171). While it was initially thought that increased nonesterified fatty acids (NEFA) concentration were the prime actors in lipid-induced insulin resistance, it is now generally admitted that both high NEFA and high plasma triglyceride concentrations are related to insulin resistance (195).

Several studies have pointed to the deleterious effect of fructose on glucose metabolism and insulin sensitivity. Indeed, a high-fructose diet increased glucose and insulin responses to a sucrose load (89), increased fasting glycemia (130), and led to hepatic insulin resistance in healthy men (76). Insulin resistance is closely linked to lipid metabolism disorders; more specifically, insulin-resistant subjects have higher ectopic lipid deposition, which may generate toxic lipid-derived metabolites, such as diacylglycerol, fatty acyl CoA, and ceramides. The presence of these metabolites in the intracellular environment leads to a higher serine/threonine phosphorylation of insulin receptor substrate-1 (IRS-1), which has been shown to reduce insulin signaling (195).

In rodent models, high-fructose or high-sucrose diets were clearly associated with the development of insulin resistance and with disturbed glucose homeostasis. In rats fed a diet in which sucrose was substituted for starch, several alterations of glucose and lipid metabolism developed over time (156). The earliest event was an increase in hepatic triglyceride content, which could be observed already after 1 wk (158, 159, 168); at this stage, fasting hormone and substrate concentrations were not changed, nor was body composition. There was however an impaired suppression of endogenous glucose production, indicating hepatic insulin resistance (158, 159, 168). Between 2 and 5 wk, fasting hyperinsulinemia developed, indicating whole body insulin resistance. The decrease in insulin's actions could indeed be documented by euglycemic, hyperinsulinemic clamps, showing a decreased insulin-mediated glucose disposal after 8 wk. This sucrose-induced insulin resistance was independent of changes in body composition. The mechanism in rodents may involve alteration of postreceptor insulin signaling. Indeed, sucrose did not alter the amount of insulin receptor, IRS-1 or IRS-2, or phosphatidylinositol 3-kinase (PI3K) in hepatocytes; phosphorylation of insulin receptors upon expo-

sition to insulin was not altered, but phosphorylation of IRS-1 and IRS-2 was reduced, indicating that sucrose impaired postreceptor insulin signaling; unexpectedly, PI3K activity was increased, suggesting a possible compensatory mechanism (157). In skeletal muscle of rats, both a high-sucrose diet (73) and a high-fructose diet (73) decreased insulin-induced insulin receptor and IRS-1 phosphorylation. This effect was observed only in living animals but was not reproduced when measuring insulin-mediated glucose disposal of isolated muscles, indicating that the effect of fructose on muscle required the living environment (115).

Although, in most studies, fructose elicited both hepatic insulin resistance and altered hepatic/extrahepatic lipid metabolism, some observations suggest that these two effects may be distinct. Thus, in healthy males, fructose overfeeding increased hepatic de novo lipogenesis and plasma triglycerides and decreased hepatic insulin sensitivity; under such conditions, supplementation with fish oil, which inhibited de novo lipogenesis, efficiently reduced plasma triglycerides but failed to normalize hepatic insulin sensitivity (76). Moreover, a high-fructose diet increased intrahepatic lipid deposition in humans, while hepatic insulin sensitivity remained unchanged (121). In rats, a diet rich in fructose and trans fatty acid also causes hepatic insulin resistance and hepatic steatosis, but here also, fructose appears more related to hepatic insulin resistance while trans fats were more involved in the development of steatohepatitis (209).

It was further observed that sucrose elicited stress responses in hepatocytes, which involved activation of the c-Jun terminal kinase (JNK). Changes in the redox state of the cells upon exposure to sucrose may be responsible for this activation of JNK. Furthermore, normalization of JNK activity in hepatocytes isolated from sucrose-fed rats normalized insulin signaling. In addition, it was documented that the effects of sucrose on JNK activity and insulin sensitivity in the liver were essentially due to the fructose component of sucrose (236–238). Fructose administration was also shown to exert a marked oxidative stress on the organism (37). Providing fructose with honey, which is naturally rich in antioxidant substances, prevented both the oxidative stress induced by fructose and the reduction of insulin sensitivity (38).

Fructose may also possibly decrease insulin sensitivity through changes in the gut microbial flora and/or alterations of intestinal permeability. It is now recognized that insulin resistance in obese patients is associated with markers of inflammation, such as C-reactive protein or proinflammatory cytokines, and with inflammation of adipose tissue (86). Recently, it was observed that a high-fat diet can lead to enhanced intestinal permeability and alterations of intestinal bacterial flora, thus resulting in an increase of the plasma concentration of bacterial lipopolysaccharides, or endotoxin. Low-grade endotoxinemia

in turn activates inflammatory pathways and impairs insulin's action, leading to the development of insulin resistance (39, 40). As for a high-fat diet, a high-fructose diet was shown to increase plasma concentrations of endotoxin (212). Furthermore, mice fed a high-fructose diet were protected against both endotoxinemia and fatty liver infiltration by an antibiotic treatment, suggesting that part of the metabolic effects of fructose were mediated by changes in the microbial flora (20).

In summary, there is no doubt that high-fructose feeding can cause insulin resistance in rodents. The evidence in humans is less impressive: fructose produces a slight impairment of hepatic insulin's actions, but does not reduce whole body insulin sensitivity. Interactions between fructose and fat or total energy intake remain to be assessed. Regarding the mechanisms possibly linking fructose to insulin resistance (Fig. 6), altered lipid metabolism and lipotoxicity secondary to stimulation of de novo lipogenesis, or fructose-induced oxidative stress may be involved. In addition, fructose may impair endothelial function through increased uric acid production, thus contributing to so-called "prereceptor" insulin resistance (see sect. IIIC).

D. Effects of Fructose Overfeeding Versus Glucose Overfeeding

The intake of naturally occurring free fructose with fruits and honey is relatively low in our western-type diet and accounts for only ~15% of total fructose intake in the United States (135). Under everyday life conditions, fructose is essentially consumed as sucrose, with the corollary that fructose and glucose intake vary in parallel. This
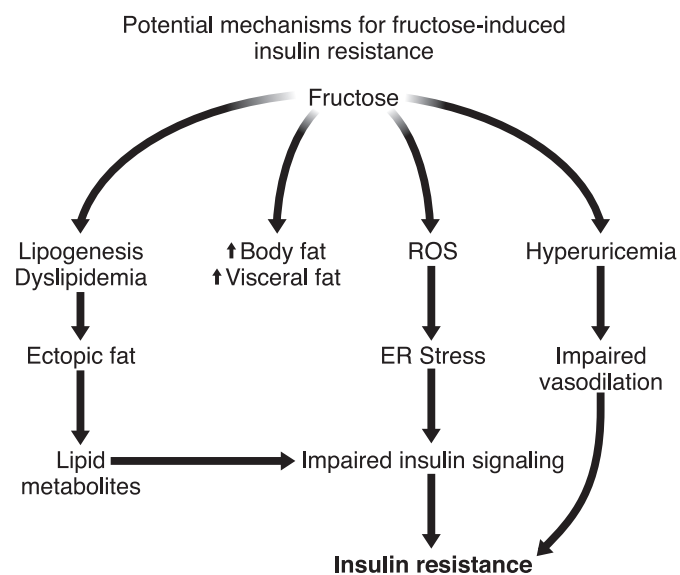

FIG. 6. Summary of the potential mechanisms for fructose-induced insulin resistance.

makes it difficult to sort out the effects of increased fructose intake versus increased glucose or total sugar intake. Several studies have however addressed the effects of short-term glucose versus fructose overfeeding in humans. One study assessed the early (30 and 60 min) response to an acute 60 g glucose load in young women fed a weight-maintaining diet containing 41% of total energy as glucose or sucrose. Plasma glucose responses were comparable with both high-glucose and high-sucrose diets and were not different from a control diet with low sugar intake. Both diets increased plasma insulin responses to the same extent, but the difference reached statistical significance only after the sucrose diet (114). In normal-weight and obese women overfed with 50% glucose, fructose, sucrose, or fat above their energy requirement, fat balance measured by indirect calorimetry was positive and identical under all three conditions; this indicated that fat storage was directly dependent on energy intake and that fructose or sucrose had no specific effect to promote fat deposition (142). De novo lipogenesis was also measured in the women overfed with glucose or sucrose and was found to be identical under both conditions (141). There was also no significant difference in plasma glucose, triacylglycerol, or insulin concentrations. De novo lipogenesis was shown to be stimulated more with acute fructose than glucose ingestion (165). However, increasing the carbohydrate content of weight-maintaining diets by administration of short glucose polymers (98), but not complex carbohydrate (101), was reported to increase fasting hepatic de novo lipogenesis. The stimulation of fasting de novo lipogenesis was of the same magnitude with high-carbohydrate diets based on glucose polymers (98) or on sugar-starch at a 60:40 ratio (98) administered over 2–4 wk. This indicated that stimulation of hepatic de novo lipogenesis may be more related to the carbohydrate load as simple sugars than to the fructose load.

Finally, the effects of a 10-wk supplementation with either glucose or fructose (in amounts corresponding to 30% of total energy requirements) were observed in a group of overweight and obese women (199). In this group of patients, glucose and fructose overfeeding led to similar body weight gains, suggesting that the lower leptin secretion induced by fructose compared with glucose (207) did not result in a larger food intake in the long term. As expected, fructose led to higher postprandial triglyceride concentrations than glucose. Furthermore, fructose, but not glucose, decreased glucose tolerance and increased the plasma concentration of small dense LDL and of oxidized LDL, which are lipid particles associated with a high atherogenic risk. However, and in contrast to the above-mentioned studies (98, 141, 142), only fructose, but not glucose, stimulated hepatic de novo lipogenesis. Of particular concern, fructose increased significantly visceral fat. From these studies, it therefore appears that overfeeding with simple sugars has several

potentially harmful effects and that the effects of fructose are more focused on alterations of hepatic lipid metabolism and of plasma lipid profile, while both sugars may contribute to lipotoxicity by promoting weight gain and increasing hepatic de novo lipogenesis.

E. Uric Acid Metabolism

In the liver, fructose loading, due to its rapid phosphorylation to fructose 1-P, drastically stimulates ATP hydrolysis, with a subsequent increase in AMP. This in turn leads to increased uric acid synthesis (176). It was indeed repeatedly observed that plasma uric acid concentrations were increased by a high dietary fructose intake. The third NANHES report indeed indicates that consumption of sugar-sweetened beverages is significantly associated with plasma uric acid concentrations (45). Furthermore, fructose consumption has been directly related to the occurrence of diseases related to uric acid metabolism, i.e., gout (44) and kidney stones (206).

Hyperuricemia is frequently encountered in patients with the metabolic syndrome and was a minor criterion for the diagnosis of "syndrome X," or "insulin resistance syndrome" in its initial description by Reaven (174). Although the mechanisms underlying the link between insulin resistance and hyperuricemia remain poorly defined, serum uric acid concentration appears to be a risk factor for the development of type 2 diabetes (61).

Recently, a novel hypothesis was proposed to link fructose intake, hyperuricemia, and insulin resistance. Insulin-induced glucose utilization involves not only the stimulation of key metabolic pathways in insulin-sensitive cells, but also an increase in blood flow and nutritive circulation to the major insulin-sensitive tissue, skeletal muscle (18). This effect of insulin is due to the activation of the endothelial enzyme nitric oxide synthase (eNOS) by insulin (200). In obese subjects, the ability of insulin to produce muscle vasodilation is impaired, and this is thought to contribute to altered glucose homeostasis through "prereceptor" insulin resistance (201). Since eNOS is potently inhibited by uric acid, it was proposed that inhibition of the vascular effects of insulin by uric acid was involved in fructose-induced insulin resistance. In support of this hypothesis it was reported that, in rats fed a high-fructose diet, both hyperuricemia and insulin resistance develop simultaneously. Furthermore, the development of insulin resistance was prevented by lowering uric acid concentrations with an uricosuric agent (149).

Intriguingly, it was recently reported that putative new fructose transporters, SLC2A9 (GLUT9), bear relationships with uricemia. These transporters, expressed in renal tubules, may possibly modulate renal uric acid excretion. Polymorphisms of *SLC2A9* have been shown to be associated with an increased fractional excretion of

uric acid, suggesting that these polymorphisms may effectively modulate uric acid excretion. Furthermore, genetic variations of SLC2A9 appear to be responsible for ~1–2% of the variance of plasma uric acid concentration in males and 5–6% in females (32, 124). Whether the initial expectation that SCL2A9 were fructose carriers, and their role in uric acid metabolism is merely coincidental, or whether these molecules are involved in some yet unidentified link between fructose and uric acid metabolism, remain presently unknown.

F. High Blood Pressure

In rats, high-fructose feeding has been also shown to be associated with the development of hypertension (102, 104). Several putative mechanisms can be proposed for this effect of fructose. As mentioned in the former sections, chronic, high-fructose feeding is associated with the development of insulin resistance. Insulin resistance, and the ensuing hyperinsulinemia, are in turn associated with high blood pressure (173). An increased sympathetic nervous system activity, possibly triggered by hyperinsulinemia, has been invoked as a potential mechanism (103, 175). Hyperinsulinemia may also increase blood pressure by enhancing kidney sodium reabsorption (179). Finally, high-fructose intake leads to a build up of intracellular glyceraldehyde and dihydroxyacetone phosphate, which can be further converted into methylglyoxal, a highly reactive ketoaldehyde. Aldehydes are able to react nonenzymatically with sulfhydryl groups of protein, thus altering their function. Of interest, aldehydes can impair the function of L-type calcium channels, and this may possibly lead to an increased intracellular calcium concentration in vascular smooth muscle, and to an increase of vascular resistance (231). Furthermore, it has been suspected by some investigators that hypertension may rather be related to deficiency in magnesium or copper of experimental high-fructose diets rather than to fructose feeding per se (37, 79).

Although there are numerous reports of fructose-induced hypertension in rodents, the link between fructose intake and high blood pressure in humans is mainly indirect. In healthy normal-weight subjects (122) and in overweight subjects (199), supplementation with fructose in doses amounting to 30% of total energy requirements failed to significantly alter blood pressure. High fructose intake may be linked with high calorie intake and weight gain, and with insulin resistance, and all these factors are themselves associated with high blood pressure. There is, however, little evidence that fructose per se directly increases blood pressure. There is ample evidence that glucose intake acutely stimulates sympathetic activity. This has been shown to be related to the increase in insulin concentration elicited by glucose rather than to

hyperglycemia per se (22, 23, 234). Furthermore, it was demonstrated that, contrary to glucose, acute fructose administration does not elicit an increase in sympathetic activity (234). When the effect of acute oral loads of glucose and fructose were compared, it was observed that fructose, but not glucose, led to a significant, although small increase in blood pressure (34). Both glucose and fructose increased heart rate and cardiac output, but glucose in addition decreased peripheral vascular resistance, which prevented an increase in blood pressure (34). It was also shown that an intravenous infusion of glucose, but not fructose, causes muscle vasodilation (234), through an insulin-mediated nitric oxide release in endothelial cells (200).

The absence of a stimulation of the sympathetic nervous system after acute fructose loading in humans (228, 234) contrasts with numerous reports of increased sympathetic activity in rodents fed a high-fructose diet (192, 246). This is likely due to the fact that chronic high fructose intake in rodents is generally associated with increased adiposity and that body fat mass is a major determinant of sympathetic activity (187).

G. Mineral Metabolism

Fructose readily forms complexes with metal ions and hence may modulate the intestinal absorption and bioavailability of minerals (152). Compared with starch, both sucrose and fructose decrease copper absorption in rats (112). A diet containing up to 20% energy as fructose had, however, no adverse effect on copper balance in humans (177). Fructose also increases iron absorption in rats (177). There was a specific concern that sugar intake may negatively impact calcium balance and bone health (222). When the effects of different types of carbohydrates were assessed in rats, it was observed that glucose and sucrose, but not fructose alone, tended to have adverse effects on bone health. Rats provided with the glucose-sweetened beverages had reduced femur and tibia total phosphate, reduced phosphate and calcium intake, and increased urinary calcium excretion compared with the rats provided the fructose-sweetened beverage. These results suggest that fructose is not directly involved in the negative association that was observed between sugar intake and bone health (223).

IV. DOES FREE FRUCTOSE EXERT DIFFERENT EFFECTS THAN FRUCTOSE BOUND TO SUCROSE?

An increase in fructose consumption has been proposed as a major contributor to the increased prevalence of obesity that was observed over the past decades worldwide. This hypothesis rests on the fact that the increase in

fructose consumption over time roughly parallels the increase in the prevalence of obesity. Much confusion arises from the fact that free fructose, i.e., under the form of HFCS or of pure fructose added as a sweetener, is often considered separate from total fructose, i.e., the sum of free fructose and fructose bound to glucose. As mentioned earlier, total sugar, including sucrose and HFCS, increased by ~15% over the past 30 years in the United States; at the same time, HFCS consumption increased dramatically and replaced a substantial amount of dietary sucrose. It results that consumption of free fructose increased markedly, while at the same time consumption of fructose bound to glucose decreased. This has sometimes led to the speculation that free fructose may have more deleterious effects of its own.

Few studies have specifically addressed the effects of free versus bound fructose. In animals, feeding a diet rich in HFCS elicited all the effects observed after high-fructose or high-sucrose diets, i.e., increased weight, dyslipidemia, and insulin resistance. As for fructose, HFCS feeding elicited an endoplasmic reticulum stress response in hepatocytes. The effects of HFCS appeared therefore qualitatively comparable to those of sucrose, but no direct comparison was made (48, 209). In patients with type 2 diabetes, administration of 35 g of sucrose or equivalent amounts of fructose and glucose as HFCS elicited similar glucose and insulin responses (6). HFCS also produced the same glucose, insulin, ghrelin, and leptin than sucrose in healthy female volunteers (143). In another study, HFCS, sucrose, and equimolar glucose-fructose mixtures elicited similar satiety responses (7) or energy intake at a subsequent meal (197). HFCS also produced an increase in 24-h plasma triglyceride similar to that observed with pure fructose (198). Although the studies comparing HFCS with sucrose remain to be completed with other end points such as lipogenesis, intrahepatic lipid accumulation, stimulation of inflammation, and with longer duration of administration, there is to date no evidence that the effects of free fructose differ from those of fructose bound to glucose.

V. DOES FRUCTOSE PLAY A ROLE IN THE PATHOGENESIS OF METABOLIC DISEASES?

In view of the compelling evidence that high fructose intake can induce, not only in animal models, but also in humans, a whole range of metabolic and cardiovascular alterations, it is legitimate to wonder whether fructose consumption plays a significant role in the pathogenesis of metabolic diseases in our populations.

Verification of this hypothesis however requires *1*) that the fructose intake in the population be quantitatively evaluated, *2*) that epidemiological data support a link between dietary fructose intake and disease (by showing

an increased odds of developing the disease at high fructose intake), and/or *3*) that intervention studies are consistent with a pathogenic role of fructose, either by showing that increasing fructose intake increases the disease or markers of the disease, or by showing that reducing fructose intake improves the disease or risk factors for the disease.

Although data on fructose consumption are available and reliable in some countries, accurate information is lacking in most parts of the world. Furthermore, many epidemiological studies did not assess directly the effects of total fructose consumption, but of "sugars" or sweet beverages. As a consequence, the information required is only partially available but is nonetheless useful to evaluate the link between fructose and diseases.

A. Fructose and Energy Intake

To evaluate the relationship between fructose consumption on one hand, and obesity and metabolic disorders on the other hand, the effect of fructose on total energy intake is an important issue. On the basis of small studies, it can be expected that fructose does not elicit satiating signals to the same extent as glucose, and hence that it may lead to uncontrolled, excessive energy intake (see sect. IIG). Several studies that assessed the relationship between soft drink consumption and energy expenditure were included in a recent meta-analysis. The conclusion was that soft drink intake was clearly associated with increased energy intake. Soft drink intake also was associated with lower intakes of milk and calcium (230).

B. Fructose and Body Weight

Several cross-sectional studies have assessed the relationship between consumption of sugar-sweetened beverages and body weight and were reviewed recently (71). Many of these studies were performed on children and adolescents. Most of these studies (13, 21, 84, 128, 132, 188, 220, 240) showed a positive association between sugar-containing drink consumption and body weight, but others failed to show such association (29, 81, 120, 182). These studies have to be interpreted with caution, however, because soft drink consumption is influenced by several factors, such as socioeconomic status, education, etc. Furthermore, soft drink intake can be associated with a different pattern of physical activity, or a different pattern of feeding. Several cross-sectional studies even showed an inverse relation between total sucrose consumption (from all sources) and body weight (31, 134), which certainly cannot be held as an indicator that sugar consumption promotes weight loss, but is rather explained by other uncontrolled variables; among a pediatric population, it was shown that high-sugar consumers

ate less fat and meat than low-sugar consumers (77). In addition, consumption of sugar-sweetened beverages may be associated with alteration of the consumption of other beverages, such as tea, coffee, or milk, with possible health consequence. For instance, replacing milk with soft drinks may have deleterious effects on calcium metabolism and bone health (8, 119, 230).

Meta-analyses linking body weight and soft drink consumption also yield conflicting results. One such meta-analysis of 88 published studies reported a significant positive association between soft drink consumption and body weight (230), while another meta-analysis of 12 studies showed no such association (80).

Intervention studies provide a clearer view of the relationship between sugar-containing beverages and body weight. In a few experimental studies, sugar-containing diets were added to the usual, ad libitum, diet. In one study, addition of beverages sweetened with HFCS or aspartame, a non-calorie-containing sweetener, resulted in a significant weight gain with HFCS-sweetened beverages only (215). In another study, overweight subjects receiving sugar-containing beverages increased significantly their energy intake and gained weight, while subjects who received non-caloric-sweetened drinks as a control did not change weight (169). Conversely, several studies, mostly performed on children and adolescents, reduced the daily intake of sugar-sweetened beverages; they all showed a significant reduction in energy intake and/or body weight (11, 68, 72, 184, 244).

C. Fructose Intake and Diabetes

Few studies have specifically evaluated the relationship between sugar intake and the risk of developing diabetes. The Women's Health Study is a prospective study in which 39,345 women aged >45 yr were enrolled and followed prospectively, while receiving either low-dose aspirin and vitamin E or placebo. Although the primary aim of the study was to evaluate the incidence of cancer and cardiovascular diseases, each participant provided detailed dietary information which allowed the evaluation of the impact of sugar intake on the subsequent risk to develop type 2 diabetes. The relative risk of diabetes was not different when the lowest and highest quintiles of sugar intake were compared. Furthermore, this absence of increased relative risk was also observed when the analysis was restricted to fructose intake (108). The Nurse's Health Study includes 121,700 registered nurses aged 30–35 yr at inclusion, who provided detailed information by questionnaires regarding diet, life-style, and medical history. Of these, 71,346 were nondiabetic at inclusion and had provided all information required to evaluate the relationship between fruit and fruit juice consumption and subsequent incidence of diabetes. The

results indicate that fruit (and vegetable) intake was associated with a lower incidence of diabetes, while consumption of fruit juice tended to be associated with a higher incidence (19). The Finnish Mobile Clinic Health Examination Survey included 51,522 nondiabetic men and women, aged 40–60 yr, from several regions of Finland and collected dietary and life-style information by interviews and questionnaires. Combined intake of glucose and fructose was associated with an increased risk of diabetes, as was consumption of sweetened fruit juices and soft drinks (146). In another study including 59,000 Afro-American women, the incidence of diabetes was significantly associated with sweetened beverage consumption, but this association was almost entirely mediated by effects of drink consumption on body weight (160). In the Nurses' Health Study II, 51,603 women free of diabetes were included, and a complete dietary assessment was obtained. The risk of gaining weight and of developing type 2 diabetes over an 8-yr follow-up period was significantly increased in women who consumed one or more sugar-sweetened beverages per day (188).

Another study examined, in 2,500 subjects of the fifth Framingham Offspring study (1991–1995), the relationship between sweetened beverage intake and surrogate markers of insulin resistance. Consumption of sweetened drinks was positively associated with fasting insulin concentrations, but not with fasting glucose concentration or with an insulin sensitivity index calculated from fasting glucose and insulin concentrations (245).

D. Fructose Intake and Cardiovascular Risk Factors

In the Framingham Heart Study, the relationship between soft drink consumption and cardiovascular risk factors was evaluated in 6,039 participants. Consumption of more than one can of soft drink per day was significantly associated with the prevalence of the metabolic syndrome, defined by three or more of the following: high blood pressure, waist circumference >35 inches (females) or 40 inches (males), high fasting plasma glucose, high plasma triglyceride, and low HDL-cholesterol. Furthermore, upon prospective follow-up of individuals without the metabolic syndrome at inclusion, consumption of more than one soft drink per day was associated with an increased risk of developing the metabolic syndrome (65).

In a study of 74 6- to 14-yr-old Swiss children, it was observed that overweight children had a similar total fructose intake as normal-weight children, but consumed a significantly higher percentage of fructose from sweets and sweetened drinks. In this population, fructose intake was associated with an increased concentration of small, dense LDL particles known to be associated with a high atherosclerotic risk (4).

Finally, the relationship between sweetened drink intake and the occurrence of coronary heart disease was assessed in 88,520 women enrolled in the Nurse Health Study. Sweetened beverage consumption was significantly associated with an increased incidence of heart disease. A major portion of the relationship was, however, mediated by effects on body weight. The relationship between sweetened beverage intake and incidence of coronary disease remained significant after adjusting for body weight and could be ascribed either to the higher glycemic index or to the high fructose content of sweetened beverages (83).

Over the past decades, several "novel markers" of cardiovascular risk have been identified. These include, amongst others, inflammatory mediators or cytokines, factors related to coagulation and fibrinolysis [such as plasminogen, tissue plasminogen-activator inhibitor-1 (tPAI-1), thrombomodulin], markers of oxidative stress, and markers of endothelial dysfunction (140, 178). In one study including 12 patients with nonalcoholic fatty liver disease and 6 healthy controls, tPAI-1 was positively correlated with total carbohydrate intake, with sucrose intake, and with fructose intake (212). Another study assessed, in 207 men and women aged 18–39 yr, the prevalence of increased novel risk markers (adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, cytokines such as tumor necrosis factor-α or interleukin-6, markers of oxidative stress, adipokines, and many others). Several of these markers were positively associated with sucrose intake (213).

E. Fructose Intake and Nonalcoholic Steatohepatitis

Few studies evaluated the relationship between fructose or sucrose consumption and hepatic fat deposition. One study evaluated whether fructose, at levels of intake usually encountered in the population, may play a role in the deposition of intrahepatic lipids. It was observed that fructose intake was nearly twice as high (~90 g/day) in patients with NAFLD than in patients without hepatic steatosis (~45 g) (155). In another study, the consumption of sweetened beverages was found to be increased in patients with nonalcoholic fatty liver disease compared with healthy controls (12). In this group of subjects, consumption of sweetened beverage was the best predictor of intrahepatic fat estimated with ultrasonography.

F. General Conclusions Regarding Epidemiological Studies

Altogether, epidemiological studies at this stage provide an incomplete, sometimes discordant appraisal of the relationship between fructose or sugar intake and metabolic/cardiovascular diseases. Part of the discordances may be explained by the fact that intakes of sugar, fructose, fruit juices, or sweetened beverages were often not recorded individually, which precludes an accurate calculation of total fructose intake. In addition, fructose is essentially consumed as either sucrose or HFCS, with the consequence that glucose intakes essentially varies with fructose intake. Confounding factors (i.e., interrelationship between sugar intake and intake of other nutrients, association with physical activity and life-style) are important and difficult to control for. At present, there appears to be strong evidence that consumption of sweetened beverages is associated with obesity, at least in children and adolescents. There is at present not the single hint the HFCS may have more deleterious effect on body weight than other sources of sugar. Regarding the relationship between fructose or sucrose intake and cardiovascular risk factors or type 2 diabetes, the evidence is even sparser. Given the number of confounding variables, there is clearly a need for intervention studies in which the fructose intake of high fructose consumers is reduced to better delineate the possible pathogenic role of fructose. At present, short-term intervention studies however suggest that a high-fructose intake consisting of soft drinks, sweetened juices, or bakery products can increase the risk of metabolic and cardiovascular diseases. There is, however, no objective ground to support that moderate intake of fructose, or of fructose consumed with fruits or honey, is unsafe.
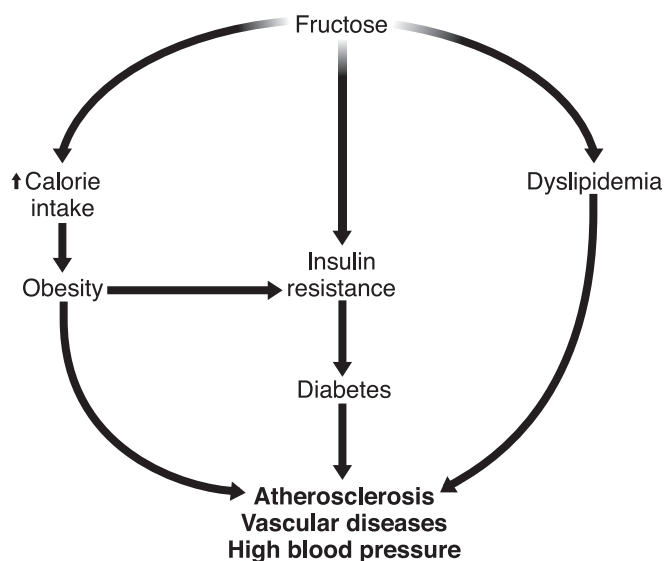

FIG. 7. Potential relationships of high fructose intake with human diseases.

VI. PERSPECTIVES

The potential danger of fructose consumption and its links to various metabolic disorders have been widely documented. Deleterious effects of high fructose intake on body weight, insulin sensitivity/glucose homeostasis, dyslipidemia, and atherosclerotic disease have been identified, and potential mechanisms have been proposed (Fig. 7). These effects, in humans, were often documented at very high levels of fructose intake, however, and some important questions remain to be addressed. Among the numerous deleterious effects of fructose, which ones are directly relevant for human daily nutrition? Most human studies addressing specifically the effects of fructose have administered large doses, often as a supplementation to an isocaloric diet. Nevertheless, there is solid evidence that fructose, even at moderate doses, can cause hypertriglyceridemia. Moreover, although data are scarcer, the fact that fructose may increase intrahepatic lipids and lead to insulin resistance in experimental settings raises some concern. Studies aimed at delineating the dose threshold at which fructose starts to chronically exert such effects remain to be performed. In addition to that, in everyday life, fructose cannot be blamed as the only culprit for all metabolic disorders. Indeed, a high fructose consumption most of the time clusters with additional "risky" behaviors, such as a hypercaloric diet, a diet rich in saturated fat, or low physical activity. Thus which part of metabolic disorders can be attributed to fructose and which results from interactions with other risk factors? Long-term intervention and longitudinal studies may help bring some clues to these issues.

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