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Review Article

Central and Metabolic Effects of High Fructose Consumption: Evidence from Animal and Human Studies

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A B S T R A C T

Fructose consumption has increased dramatically in the last 40 years, and its role in the pathogenesis of the metabolic syndrome has been implicated by many studies. It is most often encountered in the diet as sucrose (glucose and fructose) or high-fructose corn syrup (55% fructose). At high levels, dietary exposure to fructose triggers a series of metabolic changes originating in the liver, leading to hepatic steatosis, hypertriglyceridemia, insulin resistance, and decreased leptin sensitivity. Fructose has been identified to alter biological pathways in other tissues including the central nervous system (CNS), adipose tissue, and the gastrointestinal system. Unlike glucose, consumption of fructose produces smaller increases in the circulating satiety hormone glucagon-like peptide 1 (GLP-1), and does not attenuate levels of the appetite suppressing hormone ghrelin. In the brain, fructose contributes to increased food consumption by activating appetite and reward pathways, and stimulating hypothalamic AMPK activity, a nutrient-sensitive regulator of food intake. Recent studies investigating the neurophysiological factors linking fructose consumption and weight gain in humans have demonstrated differential activation of brain regions that govern appetite, motivation and reward processing. Compared to fructose, glucose ingestion produces a greater reduction of hypothalamic neuronal activity, and increases functional connectivity between the hypothalamus and other reward regions of the brain, indicating that these two sugars regulate feeding behavior through distinct neural circuits. This review article outlines the current findings in fructose-feeding studies in both human and animal models, and discusses the central effects on the CNS that may lead to increased appetite and food intake.

Keywords: Fructose, Metabolic syndrome, Appetite, Central nervous system

Introduction

As the prevalence of obesity and type 2 diabetes continues to rise, increasing attention is being directed to sugar consumption as a possible contributor to the current epidemic of metabolic disorders. A large proportion of added sugar in the Western diet is due to sugar-sweetened beverages, which have increased substantially in consumption over the last 40 years (1). Fructose is a naturally occurring monosaccharide found in fruit, honey and some vegetables. Although these foods contain only small amounts of fructose, dietary exposure to fructose most often occurs as a component of sucrose (glucose and fructose), or high-fructose corn syrup (HFCS) produced from glucose by isomerization. Varying formulations of HFCS may exist, typically either 42% or 55% fructose combined with glucose (2). Shifts in the use of fructose, and in particular HFCS, have been proposed to play a key role in the rise of metabolic disturbances in recent decades (3-7). As such, the World Health Organization (WHO) recommends that consumption of added sugars should make up no more than 10% of the daily energy intake (8).

The unique metabolism of fructose, which differs markedly from that of glucose, may hold important clues as to why fructose has been implicated in the pathogenesis of metabolic disease (9). Unlike glucose, fructose may enter the glycolysis or gluconeogenesis pathway at the trios phosphate level after bypassing the rate-limiting step catalyzed by phosphofructokinase (5, 10). This can lead to triglyceride synthesis through unchecked pathways. Furthermore, fructose is rapidly taken up by the liver due to the presence of an active hepatic enzyme system for fructose metabolism (11). Therefore, theories regarding the mechanism by which fructose may induce obesity and features of the metabolic syndrome have focused on the lipogenic nature of the sugar (6). Nonetheless, evidence linking fructose consumption to the increased prevalence of chronic diseases remains controversial. While some studies

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report positive associations between fructose consumption and metabolic disorders (4, 7, 12, 13), others report no such links between fructose consumption and components of the disease (14).

More recently, studies have focused on the role of fructose in regulating appetite and metabolism. Emerging evidence suggests that fructose may exert unique effects on the brain that differ from those of glucose. The effects of fructose on the endocrine regulators of energy metabolism and food intake are beginning to be unraveled (6). The aim of this review article/work is to highlight the current findings from fructose-feeding studies in both human and animal models, and to describe the mechanisms by which fructose may act on the central nervous system (CNS) to lead to increased appetite and food intake.

Fructose and Metabolic Syndrome

Early studies by Hwang *et al*. reported that rats, which consumed high doses of fructose (50-60%), exhibited insulin resistance, hypertriglyceridemia and hypertension (15). Since then, fructose-fed animals have been used as models for investigating acquired systolic hypertension, hepatic steatosis, and the metabolic syndrome (16-18). Studies in rodent models have shown that excess fructose intake (68% calories as sucrose) led to metabolic changes independent of increased adiposity (19). These mice developed insulin resistance, hypertriglyceridemia, and increased hepatic triglyceride content. While diets containing 68% calories from sucrose do not reflect average human consumption, recent animal studies have focused on fructose concentrations that more closely resemble an average human diet (10% w/v). These studies and others continue to demonstrate that fructose induces adverse metabolic consequences such as insulin resistance and altered lipid metabolism in both animal models and humans (7, 20, 21).

In humans, assessing the adverse effects of fructose consumption may pose additional challenges. One of the arguments surrounding fructose relates to the difficulty of separating the effects associated with consumption of excess calories from those associated with increased intake of fructose alone. In addition, long-term studies are difficult to conduct, and the results may be further confounded by differences in diet composition, metabolic status and individual variation. A common finding of the human studies conducted to date is alterations in lipid metabolism. In both animals and humans, excessive fructose consumption induces *de novo* lipogenesis (DNL) through activation of the sterol regulatory element-binding protein-1c (SREBP-1c) and the carbohydrate responsive element-binding protein (ChREBP) (5, 6, 22, 23). Nevertheless, many studies in this area suggest that the contribution of fructose to free fatty acid (FFA) and very low-density lipoprotein (VLDL) production may be small (24). For example, no differences in the liver fat were observed in the healthy individuals fed 1g/kg of fructose (25) compared with the subjects consumed 30% of their required energy from fructose over a 4-week period (26). Even so, other studies have reported that increases in hepatic DNL (27) and ectopic fat deposition in the liver (28) were observed following excess fructose consumption.

In a long-term study of overweight individuals, comparing the consumption of cola, isocaloric milk and a sugar-free drink for 6 months, the investigators reported increased liver fat, visceral adipose tissue, blood triglycerides and total cholesterol in the individuals who were fed sucrose-sweetened beverages (28). In this study, no differences in total fat mass were observed between the case and control groups. In a crossover study of healthy subjects with a family history of type 2 diabetes (at least one parent with the disease) compared to the age-matched controls, a high_fructose diet increased fat deposition in both the liver and muscles (29). Both groups also exhibited increased fasting VLDL triacylglycerols (TGs) and decreased insulin sensitivity, though the changes in VLDL TGs were greater in the individuals with a family history of diabetes (29). In another study, overweight and obese subjects who consumed fructose-sweetened beverages for 10 weeks had significant increases in visceral adiposity and hepatic DNL compared to the group who consumed glucose-sweetened beverages (27). However, in a 4-week study comparing high-fructose with high-glucose diets in healthy subjects, although the fructose group displayed significant increase in circulating TGs, no treatment effects were observed for the liver fat, visceral fat, subcutaneous abdominal fat or intramyocellular lipids of the tibialis anterior (26). Metabolic conditions under which fructose, sucrose or HFCS increases risk factors for the metabolic disease clearly require further investigation.

Uric Acid

Unlike glucose, the metabolism of fructose generates uric acid within the liver by depleting hepatic ATP. Early studies have indicated a rise in uric acid concentration following the fructose feeding (30); chronic fructose consumption results in elevated levels of both fasting and 24-hour uric acid (31, 32). Generation of uric acid is a proposed causative factor in the ability of fructose to induce features of the metabolic syndrome (7, 33, 34). Increased plasma uric acid levels are reported in fructose-fed rats, and reducing the concentration of uric acid in these animals prevents the occurrence of hyperinsulinemia, hypertension and hypertriglyceridemia (35). Nevertheless, few studies in humans exist where fructose-containing sugars have been administered at doses realistically encountered in our diet. In a systematic review and meta-analysis of 18 controlled feeding trials, the authors concluded that the uric acid response to fructose feeding

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differed between the isocaloric and hypercaloric diets (36). Whereas hypercaloric fructose supplementation resulted in a substantial increase in plasma uric acid level, diets in which fructose was exchanged for other carbohydrates had no effect on uric acid levels (36). In congruence with these findings, data from two cross-sectional studies of adult participants illustrated that dietary fructose intake was not associated with elevated plasma uric acid levels or risk of hyperuricemia (37, 38). In contrast, two prospective cohort studies, one in men and one in women, revealed that consumption of fructose-rich beverages was associated with increased levels of uric acid and risk of gout (39, 40). Compared to women, the men had a greater increase in the risk of gout with increased fructose consumption, likely reflecting the low incidence rate of gout in the female population. Similarly, evidence from the National Health and Nutrition Examination Survey (NHANES) has also linked soft drink intake with increased uric acid levels (41).

Hyperuricemia has been linked to hypertension in many studies, and recent evidence shows that elevated uric acid levels may be an independent predictor of the development of hypertension (42). In a randomized control trial of healthy individuals, administration of a high_fructose diet (200 g fructose/day) for two weeks resulted in an increase in ambulatory blood pressure (34). This response was normalized with the concomitant administration of uric acid lowering drug (allopurinol), indicating that fructose consumption and the associated hyperuricemia resulted in elevated blood pressure (34). Despite these findings, evidence from the recent systematic review and meta-analysis by Ha *et al*. revealed that fructose had no adverse effects on blood pressure (43). Neither hypercaloric nor energy-matched feeding studies have indicated any significant effects on blood pressure in humans (43). Further work is required to better understand the association between fructose consumption and hypertension.

Central Effects of Fructose

Fructose has been found to alter biological pathways in other tissues including the CNS, adipose tissue, and the gastrointestinal system (5, 6). In the brain, both animal and human studies have indicated that fructose may disrupt endocrine signals involved in the regulation of energy metabolism. Leptin is a major regulator of energy homeostasis primarily derived from adipose tissue with central and peripheral effects on food intake and dietary substrate handling (44). Through both direct and indirect mechanisms, leptin reduces food reward (palatability) while augmenting the response to satiety signals. The gastric hormone, ghrelin, opposes the hypothalamic actions of insulin and leptin to stimulate food intake (45). In the acute setting, consumption of fructose in humans results in lower circulating insulin and leptin levels, and fails to suppress post-meal ghrelin levels as effectively as glucose, suggesting that fructose impairs energy balance signaling, and leads to decreased satiety (46). The observed decrease in leptin secretion associated with fructose consumption is supported by the/this evidence that insulin-mediated glucose metabolism plays a role in regulating leptin release (47). Conversely, long-term fructose feeding has been reported to induce hyperleptinemia in humans (25). In fructose-fed rats, increases in both leptin and ghrelin have been reported, indicating the development of leptin resistance upon high-fructose feeding (6, 48). In response to both leptin injection and a high-fat diet, prolonged maintenance of rats on a high-fructose diet resulted in leptin resistance in the absence of increased body weight or circulating leptin levels (49). This finding implies that leptin resistance precedes development of obesity, and may be an early feature of fructose-induced metabolic disorders.

Fuel sensing and appetite are controlled by the hypothalamus. A number of peripheral signals act in the brain to regulate food intake over time, a process known as energy homeostasis (45). Unlike glucose, which suppresses food intake (50, 51), fructose administered centrally at hyperphysiological doses induces increased feeding (6, 50, 52). This difference is attributed to the inverse effect on the level of hypothalamic malonyl-CoA between the two sugars (52). In the brain, malonyl-CoA is a key intermediate that serves to modulate energy balance by signaling the anorexigenic-orexigenic neuropeptide system to suppress food intake (6). In the CNS, bypassing the rate-limiting step of glycolysis catalyzed by phosphofructokinase allows fructose to be metabolized more quickly than glucose. As a consequence of the rapid consumption of ATP by 2-ketohexokinase to phosphorylate fructose, centrally-administered fructose leads to a decrease in ATP. Decreased ATP levels are associated with an increase in AMP levels, activation of AMP kinase (AMPK), inactivation of acetyl-CoA carboxylase (ACC) and lowered malonyl-CoA concentration, thus leading to increased food intake. Moreover, central administration of fructose impairs the appetite suppressing effects of the glucagon-like peptide 1 receptor (GLP-1R) (53). The mechanism by which GLP-1R reduces food intake involves inhibition of central AMPK, and fructose counteracts the inhibition of hypothalamic AMPK by GLP-1R agonists (53). In contrast to the effects of centrally-administered fructose, fructose consumed as an oral sugar solution showed no difference in food intake when compared with either glucose or sucrose solutions in human subjects (54); all of the three sugars showed similar effects on food consumption when provided to animals in drinking water (48). Interestingly, intermittent exposure to fructose resulted in bingeing behavior in rats, where bingeing was defined as consumption of a large sugar meal within the first hour of food presentation (55). In this study, fructose

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bingeing was shown to alter the activity of neurons in the nucleus accumbens (NA) shell and orexin neurons in the lateral hypothalamus/perifornical area, areas of the brain containing pleasure-driven mechanisms.

Several studies have indicated that changes in the hypothalamic malonyl-CoA expression are associated with changes in the expression of appetite-regulating neuropeptides α-melanocyte-stimulating hormone (α-MSH), cocaine- and amphetamine-regulated transcript (CART), proopiomelanocortin (POMC), neuropeptide Y (NPY) and agouti-related peptide (AgRP) (51, 56-58). In the food deprived-state, the orexigenic neuropeptides (NPY and AgRP) are expressed at high levels, whereas the anorexigenic neuropeptides (α-MSH, CART and POMC) are expressed at low levels (51). This pattern is reversed upon refeeding. In fasted mice, centrally-administered glucose decreases the expression of NPY and AgRP in the hypothalamus, and increases the expression of α-MSH, POMC and CART (51, 52). When glucose-treated mice are provided access to food, food intake is significantly reduced within 30 minutes following infusion (51). On the other hand, centrally-administered fructose decreases POMC mRNA, suggesting a rise in food intake (52). However, this effect is dependent on the ability of fructose to cross the blood-brain barrier. Fructose feeding has been demonstrated to increase the expression of fructose-sensitive glucose transporter (Glut5) in the brains of adult rats (59). Moreover, fructose is metabolized in microglia of the hippocampus (59) and Purkinje cells in the cerebellum (60); others have indicated that fructose administered systemically may cross the blood-brain barrier, and undergo metabolism in the hypothalamus (61, 62).

More recently, animal studies investigating the CNS effects of fructose on appetite control have been extended to humans. Using the arterial spin labeling of functional magnetic resonance imaging (fMRI) technique, Page *et al*. (63) measured the cerebral blood flow in adult subjects before and after consumption of either a glucose or fructose preparation. Notably, the hypothalamic cerebral blood flow, an indirect marker of neuronal activation, was markedly different following fructose ingestion when compared to glucose. Whereas glucose ingestion was followed by a decrease in the hypothalamic activity (63-65), ingestion of fructose not only failed to suppress the hypothalamic activity but also produced a small transient increase in the activity of this brain region (63). Moreover, consumption of fructose did not result in deactivation of the striatum, a response that normally occurs in association with satiety. The cortical structures (i.e. rostral anterior cingulate and anterior insula), implicated in higher-order control functions, also exhibited varying activation patterns following the ingestion of fructose and glucose (63). Contrary to the observations by Page *et al.*, Purnell *et al.* did not detect significant changes in the hypothalamic activity during the intravenous administration of either glucose or fructose (66). In this study, however, glucose and fructose doses were relatively small, and were administered intravenously; thus, differences in study design may explain the discrepant findings. In contrast to the hypothalamic findings, Purnell *et al.* did detect an increase in cortical activity during the glucose infusion and a decrease in cortical activity with fructose infusion (66). Taken together, these findings show that exposure of the human brain to fructose promotes increased food intake by modulating the brain regions involved in appetite regulation and feeding behavior.

The limbic structures central to the motivation-reward systems associated with the hedonic drive to eat are the ventral tegmental area (VTA) and NA, with inputs from other brain regions such as the striatum, amygdala, orbitofrontal cortex, insula and hippocampus (45). Although the neural circuitry regulating the food reward pathway is not completely understood, dopamine neurotransmission within the mesolimbic dopaminergic system appears to be an essential component of this process (67, 68). Specifically, dopamine signaling from the VTA to the NA in the ventral striatum mediates appetite-motivated behavior (69). When palatable foods such as sucrose are consumed, more dopamine is released from the NA (70). Obesity, however, is associated with decreased availability of striatal dopamine D2 receptors in humans (71). In fact, dopamine antagonists increase appetite, energy intake and weight gain. Both insulin and leptin have been found to modulate brain reward circuitry (72). Insulin acts centrally to diminish reward for food in animals (73), and leptin administered directly to the VTA decreases food intake in the acute setting (74). Insulin resistance induced by chronic fructose consumption may increase the drive to eat, as elevated circulating insulin levels in obese animals are associated with altered levels of dopamine release and clearance (75). Furthermore, hyperinsulinemia interferes with leptin signaling, contributes to leptin resistance (76), and is associated with greater energy intake (77). Lastly, consumption of either fructose or sucrose, but not glucose, upregulates the hypothalamic endocannabinoid receptor messenger RNA, corresponding with increased food intake. Endocannabinoids are involved in regulating the intake of sweet foods and drinks. This finding suggests that it is the fructose component of sucrose that activates reward pathways in the brain (48).

Fructose and Other Diseases

In addition to the association between excess dietary fructose and metabolic disorders, the adverse effects of its consumption have been extended to other diseases such as cancer (78) and Alzheimer's disease (79). For example, results from animal studies suggest that fructose may be linked to impaired memory and a decline in cognitive

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function (80, 81). In humans, high intake of added sugar, but not natural fructose from fruits and vegetables, was associated with decreased cognitive performance in middle-aged and older Puerto Rican adults (82). Furthermore, emerging evidence suggests that high fructose intake during pregnancy contributes to metabolic dysfunction in both the mother and fetus (83).

Conclusions

In summary, the adverse metabolic effects following fructose consumption continue to be recognized. Evidence has uncovered some of the mechanisms through which fructose exerts its effects on the CNS to disrupt energy metabolism, and lead to increased food intake. However, data supporting the weight-increasing effect of fructose remain inconsistent. Long-term trials with controlled exposure and dosage levels are required to help us further unravel the mechanisms linking high-fructose consumption and its adverse health risks.

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