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Review

Dietary fructose as a model to explore the influence of peripheral metabolism on brain function and plasticity

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ABSTRACT

High consumption of fructose has paralleled an explosion in metabolic disorders including obesity and type 2 diabetes. Even more problematic, sustained consumption of fructose is perceived as a threat for brain function and development of neurological disorders. The action of fructose on peripheral organs is an excellent model to understand how systemic physiology impacts the brain. Given the recognized action of fructose on liver metabolism, here we discuss mechanisms by which fructose can impact the brain by interacting with liver and other organs. The interaction between peripheral and central mechanisms is a suitable target to reduce the pathophysiological consequences of neurological disorders.

1. Introduction

Nutritional overload induced by high dietary intake of fats and sugars is one of the main causes of obesity [1]. Increased consumption of fructose (30% in the last 40 years) has been associated with the prevalence of metabolic syndrome (MetS) and obesity. MetS is a group of conditions that elevate risk of cardiovascular disease, stroke, and diabetes type 2, and include glucose intolerance, hypertension, and hyperlipidemia [2], and only recently neurological dysfunction have become part of the scenario [3]. Fructose (β-D-fructofuranose, $C_6H_{12}O_6$) is a functional/constitutional isomer of glucose naturally found in fruits and honey, and high fructose consumption is getting recognition as a major cause of MetS (Fig. 1).

Fructose is a natural sugar that when consumed as part of fruits, vegetables and honey has healthy benefits. For example, blueberry powder dietary supplementation, which contains a high concentration of fructose, counteracts several of the deleterious effects of brain trauma [4]. Since fructose has a chemical structure similar to glucose, and does not directly stimulate insulin secretion (mechanism deficient in diabetics), the presence of this compound in the diet produces a lower increase in blood glucose when compared to the amount of other carbohydrates [5]. Furthermore, the presence of water, fiber and antioxidants in the fruit causes fructose to be absorbed more slowly and thus tolerable to the body.

On the other hand, fructose when ingested in high concentration for a prolonged time as an additive to meals has a myriad of unhealthy consequences within the spectrum of MetS, such as obesity, systemic inflammation, and behavioral dysfunction [6]. In addition, the long-term consumption of high fructose can result in development of non-alcoholic fatty liver disease, a manifestation of MetS which is common in Western industrialized countries (6–35% prevalence, median 20%) [7]. An increasing line of clinical and experimental evidence indicates that high fructose consumption correlates with rising rates of neurologic disorders [8], such that the study of the mechanisms involved on the impact of fructose on the brain is becoming an area of intense research. Research so far indicates that fructose can affect the brain directly and/or indirectly by involving peripheral metabolism. This review will mainly discuss how fructose affects the brain via systemic physiology, as the direct effects of fructose on brain cells have been thoroughly reviewed somewhere else [9]. Most fructose is metabolized in the liver after being absorbed by the intestine to the bloodstream [8]. Given the action of liver on detoxification, synthesis of lipids and proteins essential for brain homeostasis, liver dysfunction can have devastating consequences for the brain. We are starting to understand that liver disorders such as hepatic encephalopathy have serious neurological consequences [10,11] that have been out of sight of mainstream studies. It is becoming to be understood that byproducts of fructose metabolism in the liver such as triglycerides and other lipid forms may influence brain function.

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2. Brief story of the long evolutionary history of fructose consumption

Before agriculture was developed around 10,000 years ago, hunting, gathering, and fishing were the main strategies to procure food. Food was scarce and unpredictable to obtain such that accumulation of calories in the form of adipose tissue was an important strategy to survive times of scarcity. In this context, consumption of foods high in caloric content provided to our ancestors a secure way to cope with times of rainy days. Although it is difficult to establish how much sugar our prehistoric ancestors consumed, it is plausibly that wild fruits and honey were accessible to our ancestors, particularly to those who lived in regions of warm climate and forest such as in the African continent. Nowadays, regions in Tanzania are considered living remnant of full-time hunter-gatherers, in which contemporary inhabitants live on what they find: game, plants, honey and fruits rich in fructose [12]. It is important to consider that food procurement demanded high levels of physical activity for our ancestors, and this activity seems to have provided the caloric balance necessary to maintain overall health.

The advent of agriculture approximately 10,000 years ago provided a more secure supply of foods, including fruits rich in fructose. The industrial revolution of the nineteen century represents a dramatic game changer for dietary practices as it enabled massive production of processed foods containing high levels of sugary components. In particular, high-fructose corn syrup (HFCS), main form of currently consumed fructose in the U.S., was launched to market in 1970 based on enhanced sweetness and low price. Depending on the type of HFCS, fructose occupies between 42% and 55% of its composition. Today, fructose is widely consumed in many types of processed foods and fructose appears as an important factor in metabolic and neurological disorders [9].

It has been shown that fructose exerts an impact on metabolic genes related to several metabolic disorders [13]. It is noteworthy that the genomic makeup of living individuals is the product of dietary habits occurring thousands of years ago, as mutations occur in the range of many thousands of years. Therefore, increases in fructose consumption pose a big challenge to our conservative genes, and current habits can tip homeostatic balance towards disease stages. These limitations are even more alarming when considering that sudden increases in sugar consumption post-industrialization have been accompanied by a dramatic decrease in exercise.

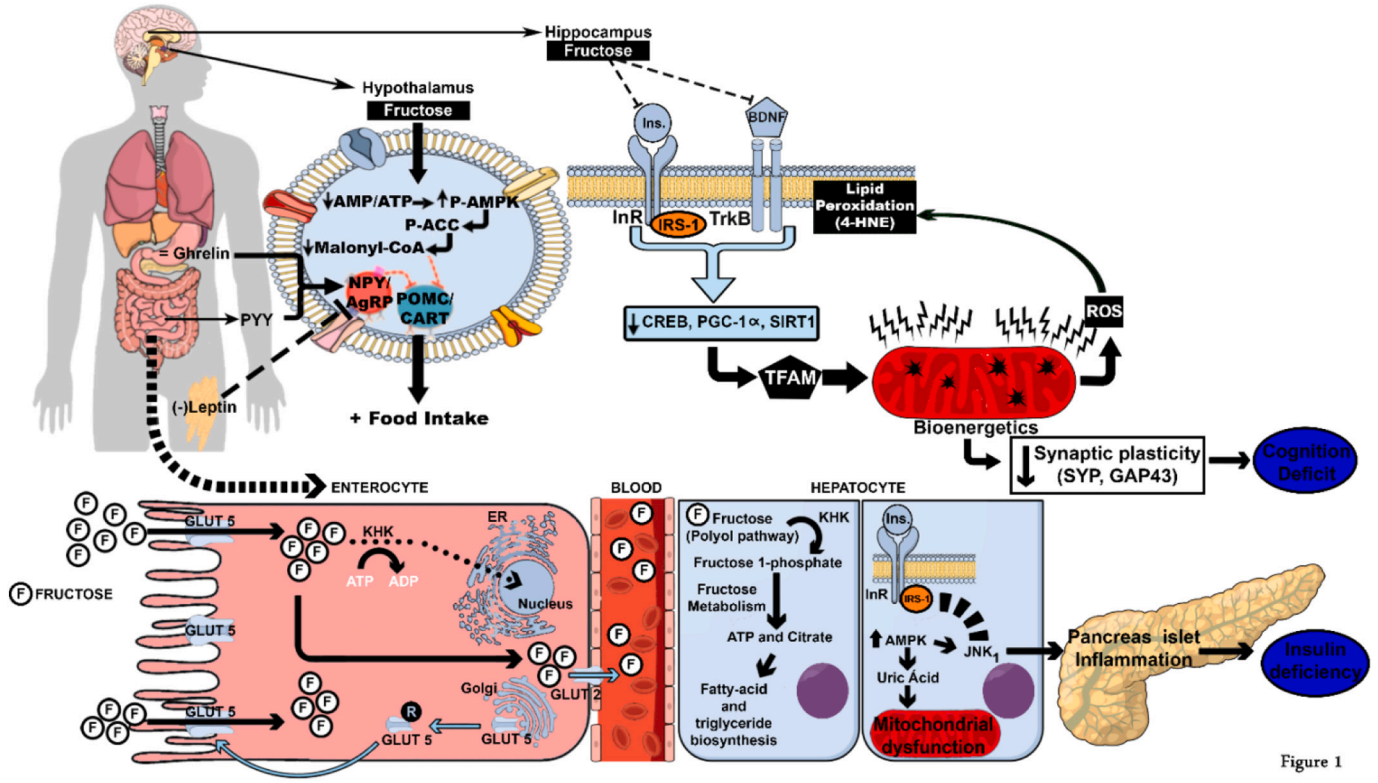

Fig. 1. Proposed mechanism by which fructose consumption affects cell metabolism in body and brain. Fructose is absorbed across the apical membrane of intestinal epithelial cells via an energy-independent mechanism, which requires the transmembrane transporter protein GLUT5. The majority of absorbed fructose enters the circulation across enterocytes via the GLUT2 transporter. Fructose consumption promotes release of appetite hormones such as peptide YY (PYY) and ghrelin. There is also increase in neuropeptide Y (NPY) and agouti-related protein (AgRP), orexigenic neuropeptides that stimulate food intake by decreasing the satiety peptide pro-opiomelanocortin (POMC) and cocaine-amphetamine-regulated transcript (CART) in arcuate nucleus of hypothalamus [108]. In the hypothalamus, high fructose elevates AMP kinase (AMPK), leading to inactivation of acetyl-CoA carboxylase (ACC) and malonyl-CoA, and increased food intake. Excessive fructose catabolism in liver also induces ATP depletion which, in turn, activates AMPK and protein c-jun-*N* terminal kinase-1 (JNK1). This protein leads to insulin resistance through the phosphorylation of IRS-1 on Serine307 residue (IRS-1Ser307). Fructose can also induce Uric Acid (UA) that inhibits pathways associated with management of cell energy metabolism in liver. High serum UA after fructose consumption causes inflammation in pancreas contributing to irregular insulin secretion. Fructose interferes with signaling of both insulin receptor and BDNF receptor inhibiting pathways associated with managements of cell energy metabolism and plasticity, such as cAMP response element-binding protein (CREB) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a), and SIRT1. PGC-1a and mitochondrial transcription factor A (TFAM) influence mitochondrial biogenesis, and they may convey the effects of fructose on decreasing oxidative phosphorylation and bioenergetics. SIRT1 modulates synaptic plasticity and memory formation via posttranscriptional regulation of CREB therefore, the interaction among SIRT1, PGC-1a, and TFAM may be important to regulate cognitive function. The loss in energy homeostasis results in ROS, and the harmful by-product of lipid peroxidation 4-hydroxynonenal (4HNE), thereby compromised plasma membrane function. Excessive consumption of fructose may result in lipid peroxidation of the plasma membrane affecting synaptic plasticity and cognition.

3. Intestine acts as a gate for fructose action on body and brain

Although isolated fructose is poorly absorbed by the intestine [14], over-consumption of fructose results in unhealthy metabolic phenotypes including increased intrahepatic fat content, decreased insulin sensitivity, dyslipidemia and adiposity [15]. In spite of the slow absorption rate of fructose by part of the intestine, excessive dietary fructose can remain in the gut for extensive time as fructose can reach up to a concentration of 2–3 mM before being utilized [5]. The fructose in the gut is transported into the enterocyte through the specific fructose transporter GLUT5, independently from ATP hydrolysis and sodium absorption. Once inside the enterocyte, fructose is transported into the bloodstream via the GLUT2 transporter [16]. It is noteworthy that excessive dietary fructose can overwhelm the absorptive capacity of the small intestine leading to incomplete absorption of fructose [17]. The non-absorbed fructose can be rapidly propelled into the colon, where its contact with the anaerobic flora causes fermentation, bloating and diarrhea [18]. It is remarkable that this action of dietary fructose on intestinal microbes can generate byproducts that influence systemic physiology and brain.

Fructose entering the enterocyte cytosol may be phosphorylated by Ketohexokinase (KHK) enzyme resulting in rapid depletion of ATP and accumulation of pyruvate and acetyl-CoA. Although these events help maintain the downhill fructose gradient into the cytosol, they also reduce intestinal Ca^{2+} [19] and inorganic phosphate (Pi) transport [20] that compromises absorption of certain minerals essential for bone health. Under normal conditions, systemic fructose concentration is relatively low (<0.05 mM) in healthy humans [21] and tissues such that liver and kidneys are sensitive to small changes in circulating fructose [2]. Excessive fructose intake also stimulates endogenous glucose production and lipid synthesis in the liver [22], events associated with the spectrum of MetS, such as obesity and systemic inflammation [6]. Regarding fructose metabolism in intestine, the enteroendocrine (EEC) cells after detecting fructose in the gut, activate a cascade of endocrine events. In particular, luminal fructose stimulates secretion of human PYY, cholecystokinin, neurotensin [23], and serotonin by secretory intestinal cells [2].

4. Fructose metabolism in liver – brain axis

A large body of literature indicates that most fructose is metabolized in the liver after being absorbed by the intestine to the bloodstream [24]. The liver is the primary organ for processing lipids and proteins, which are exported to brain and other tissues and organs. Lipids are essential for brain function and behavior, being part of plasma membranes, working as molecular transport systems, neuronal signaling systems, etc. [25]. The brain contains the second highest concentration of lipids in the human body. The metabolism of brain lipids is tightly regulated through a liver-brain interaction in which the autonomic nervous system plays a crucial role. Liver dysfunction can be aggravated by consumption of fructose as fructose is mainly metabolized in the liver where is converted into fatty acids that can reach the brain and expand the inflammatory reaction started in the periphery [27]. Fructose is metabolized in liver via fructolysis, and the primary metabolites and by-products include glucose, lactate, triglyceride, free fatty acid, uric acid and methylglyoxal. GLUT5 is widely expressed in adipose tissue, kidney, muscle skeletal tissue, testis and brain [28] that could also participate in fructose metabolism.

It can be noted that fructose metabolism differs from that of glucose since hepatic fructose is converted rapidly to triose-phosphate independently of insulin control and without a citrate feedback [16]. A large portion of fructose is converted into glucose which can be released into the bloodstream or stored as glycogen. Another portion of fructose is converted into fatty acids, which under exacerbation can contribute to the formation of hypertriglyceridemia and fatty liver disease. Furthermore, experimental long-term fructose (30% solution for 10 weeks) consumption decreases mitochondrial enzymes that catalyze β-oxidation in the liver [29]. Excessive lipid accumulation elicited by fructose in hepatocytes can also disrupt mitochondrial function [30] and elevate levels of oxidative stress and inflammation [2]. When compared with glucose, fructose overconsumption exerts divergent effects on hepatic mitochondrial function. Quantitative electron microscopy revealed that fructose but not glucose increases the number of mitochondria in the liver, and increases fission and/or decreases fusion [29]. These experimental data indicate that fructose-induced mitochondrial dysfunction may contribute to the development of fatty liver disease. Fructose consumption also induces pancreatic β-cells hyper-responsivity to glucose-stimulated insulin secretion which can affect peripheral metabolism given the extreme sensitivity of adipose and other tissues to the action of insulin [31]. The enzyme fructokinase C that rapidly phosphorylates fructose in the liver, reduces ATP, activates purine nucleotide turnover that culminates in the formation of uric acid as well as Reactive Oxygen Species (ROS) and mitochondrial dysfunction [2,32,33].

Uric acid is a waste product from the breakdown of purines in the liver that once released to the circulation can reach the brain [5]. Fructose catabolism in liver induces rapidly ATP depletion and release of uric acid to the systemic circulation resulting in hyperuricemia [28]. In situations of high fructose consumption, oxidative stress promoted by accumulation of uric acid triggers an inflammatory response in liver and extrahepatic tissues, causing inflammation and lipid accumulation [34]. Uric acid can harm the brain as seen in patients with Alzheimer's and Parkinson's disease in which uric acid acts as a risk factor for disease progression and a possible marker of cognitive dysfunction. [35]. The uric acid-mediated oxidative stress-induced lipid peroxidation causes DNA damage and activates inflammatory factors that lead to cell damage [36].

5. Effects of fructose on microbiota

The gut is the largest microbial, endocrine, and immune organ in humans and mice. The bacterial composition of the gut has emerged as profound regulator of whole-body metabolism and contributing to host immune homeostasis [37,38], and influencing brain function and disease [39–42]. Gut microbiota plays an important role in brain-gut interaction and behavior by producing metabolites, hormones and immune factors that can influence the brain [43]. Fructose affects microbiota composition and abundance that associate with metabolic dysregulation and select pro-inflammatory phenotypes in hypothalamus, liver and adipose tissues [44]. Proinflammatory microbiota and its byproducts such as LPS recruit macrophages that bind toll-like receptors leading to the release of cytokines (TNF-α) causing inflammation of the intestinal mucosa. As a consequence, there is a decrease in tight junction proteins resulting in a greater permeability of the intestinal barrier increasing the penetration of pathogens into the bloodstream [45].

6. Role of hypothalamus on regulating the action of fructose on brain-body interaction and behavior

The hypothalamus is the master center for regulation of brain and body metabolism and control of appetite and feeding behavior, and works with the hippocampus to regulate cognitive function. The hypothalamus controls all body organs via the pituitary endocrine axis and the autonomic nervous system. Fructose affects food intake by stimulating release of glucocorticoid hormones [46] which feedback on the hypothalamus. Fructose overconsumption (10% solutions), reduces total protein kinase B (Akt), Ser^{473}-phosphorylated Akt (pAkt-Ser^{473}), and insulin receptor phosphorylation in the hypothalamus [47]. Insulin inhibits the expression of neuropeptide Y (NPY) and agouti-related protein (AgRP), which are orexigenic neuropeptides that stimulate food intake in the hypothalamus. Therefore, excess of circulating insulin secondary to fructose-induced insulin resistance dysregulates energy homeostasis leading to AgRP/NPY overexpression, in association with

an increase in appetite and body weight [48].

Fructose affects appetite hormones like ghrelin, leptin and peptide YY (PYY), which are secreted in the periphery and travel via circulation to the hypothalamus. Fructose stimulates release of leptin from adipocytes and promotes leptin resistance together with an enhancement of satiety signals in the hypothalamus [49]. Leptin resistance involves Janus Kinase (JAK)-mediated phosphorylation, activation of transcription 3 (pSTAT3) functions, and impairment of leptin transport through the BBB [50]. The leptin resistance elicited by high fructose (60% solutions), can occur on the absence of body weight gain or circulating leptin levels [51]; therefore, it is possible that leptin resistance is an early feature in the chronic process of development of a fructose-induced metabolic disorder. On the other hand, a short period of fructose consumption (15% solutions) in humans has been shown to result in lower levels of circulating insulin and leptin, and fails to suppress post-meal ghrelin levels [52]. Therefore, it seems that the length and concentration of fructose intake are crucial determinants for the type of physiological response. It is notable the strong interaction between pathways that regulate food reward and metabolism in the brain, and that they become dysfunctional in metabolic disorders such as obesity [53,54].

The hypothalamus harbors neurons that express the endocannabinoid receptor 1 (CB1) [55]. The endocannabinoid system seems to play a regulatory role on the rewarding aspect of the consumption of palatable foods, and particularly high fructose [56]. Endocannabinoids levels are increased in response to fasting and are suppressed postprandially [57]. In addition, a single intravenous injection of leptin, which regulates energy balance and eliminates hunger, reduces endocannabinoid release from the hypothalamus [58]. Experimental evidence indicates that short-term (two weeks) consumption of fructose (23% solutions) but not glucose increases mRNA levels of CB1 receptor [59] and affects enzymes involved in the synthesis/degradation of endocannabinoids (anandamide and 2-arachidonoyl-glycerol) [60].

The hypothalamus plays a crucial role on the control of brain and body homeostasis. Fructose has several metabolic effects in the hypothalamus such as depletion of ATP, increase in activation of AMP kinase, inactivation of acetyl-CoA carboxylase, reduction of malonyl-CoA, together with stimulation of food intake [61,62]. Furthermore, fructose-induced hypothalamic AMPK activation increases hepatic gluconeogenesis by the elevation of circulating corticosterone level, further contributing to systemic insulin resistance [63]. Fructose but not glucose has been shown to reduce hypothalamic cerebral blood flow in healthy volunteers [64]. Ancillary, fructose is metabolized faster than glucose in the brain [55], pointing out another difference between fructose and glucose. Fructose consumption can elicit robust changes in oxidative stress in the hypothalamus. For example, high-fructose (60% solutions) consumption for 10 weeks decreases levels of antioxidant enzymes, including cytoplasmic copper-zinc superoxide dismutase 1, mitochondrial manganese superoxide dismutase 2, glutathione peroxidase, glutathione reductase, and catalase [65].

The actions of fructose on hypothalamic metabolism may be operational for regulation of metabolic disorders such as obesity, insulin resistance [48], and other disorders [6]. Using systems nutrigenomics in a rodent model of high fructose consumption, it has been reported that fructose uses the extracellular matrix biglycan gene (Bgn) to alter molecular pathways related to oxidative phosphorylation, glucose metabolism and fatty acid metabolism in the hypothalamus [13,66]. This prominent response of Bgn in hypothalamus elicited by fructose is crucial to understand how metabolic disorders (e.g. diabetes and obesity) influence brain centers.

7. Metabolic action of fructose on cognitive function – hippocampus

The hippocampus plays a preponderant role on learning and memory processing and works with the hypothalamus to integrate feeding behavior with higher order functions. The hippocampus is highly susceptible to the action of fructose such that high fructose consumption results in alterations in cognitive function [67,68]. Experimental evidence in rodents shows that overconsumption of fructose (15% solutions) for a duration (6 weeks), sufficient to disrupt peripheral metabolism reduces hippocampal insulin receptor signaling, which is commensurable to poor learning and memory performance [69]. In addition, 15% fructose by 8 weeks compromises the capacity of the hippocampus to sustain synaptic plasticity in the forms of long-term potentiation (LTP) and long-term depression (LTD), followed by reduction of synaptic contact zones and neurogenesis [70]. Even a shorter period of fructose or sucrose consumption (4 weeks, 23% solutions) but not glucose, reduces hippocampal neurogenesis [71].

Fructose consumption is currently perceived as an important cause of metabolic disorders with subsequent detriment of cognitive function. In this context, several mechanisms have been suggested for the action of fructose on cognitive function such as disruption in oxidative metabolism [56], decreases in neurotrophic factor expression, increases in oxidative stress and inflammation [72]. A comprehensive study [73] showed that high fructose consumption in rodents (15% solutions) for 6 weeks disrupts pathways associated with cell energy metabolism involving peroxisome proliferation-activated receptor gamma coactivator 1-alpha (PGC-1α), mitochondrial transcription factor A (TFAM) and sirtuin 1, and synaptic plasticity modulators such as cAMP response element-binding protein (CREB). The fact that PGC-1α interacts with TFAM on mitochondrial biogenesis [74] and SIRT-1 affects synaptic plasticity via posttranscriptional regulation of CREB [75] suggests that fructose may disrupt the interface between cell metabolism and synaptic plasticity, making the brain susceptible to neurological disorders.

Interestingly, the effects of fructose on cognition may also involve inflammatory pathways that are affected by hepatic metabolism. For example, translocation of high mobility group box 1 (HMGB1), a highly conserved non-histone DNA-binding protein, from nucleus to cytoplasm in response to high fructose consumption (30% solution) elicits an inflammatory cascade involving Toll like receptor 4 (TLR4), nuclear factor-kappa B (NF-κB) and the transcription of proinflammatory cytokines [76]. The TLR4/NF-κB signaling pathway activation elicited by HMGB1 induces apoptosis in hippocampal cells and subsequent cognitive deficits in animal models of obesity [77,78].

The overconsumption of fructose-sweetened beverages is particularly relevant to young individuals [79]. Experimental short-term fructose (20% solution for 7 days) consumption in young rodents results in increased levels of inflammatory and oxidative damage markers in the hippocampus [80]. These studies reinforce the idea that oxidative stress and inflammation play a central role in fructose-induced damage to the brain even in offspring. In turn, studies showing increases in cerebral protein nitration followed by cytochrome *c* oxidase and Citrate synthase activity in the hippocampus from adult, but not young, suggest that aging might exacerbate the oxidative condition induced by this diet [81] and this is particularly relevant since protein nitration plays a role in the progression of neurological disease [82].

8. Fructose impacts the substrates for neurological and psychiatric disorders

Chronic fructose consumption disrupts various cellular processes such as inflammation and oxidative metabolism which reduces the threshold for a range of neurological and psychiatric disorders [83]. Metabolic dysfunction is an important aspect of the pathogenesis of several neurological diseases [72]. For example, visceral fat and serum triglycerides induced by high fructose consumption have been associated with anxiety and depression-like behaviors [84]. Furthermore, it is known that fructose modulates the serotonergic system, which has important actions on the regulation of emotions and cognition [85]. Consumption of a 30% fructose diet for 8 weeks resulted in a decrease in serotonin reuptake transporter (SERT) protein levels in mouse duodenum [64]. Interestingly, SERT-deficient mice are used as a relevant

model for depression, suggesting a link between fructose consumption and psychological effects [86].

Experimental evidence indicates that consumption of a high-fructose diet (55%) starting during juvenile life promotes a pro-inflammatory state involving both the Central and Peripheral Nervous Systems, and resulting in psychiatric-like disorders in adulthood [87]. Obese phenotype in female rats caused by high fructose consumption (20% diet) is associated with an increase in IL-1β production, microglial reactivity and hyperphosphorylation of tau in the hippocampus, concomitant to neuronal loss and neurological dysfunction at 48 h post-stroke [88].

Fructose-induced insulin resistance is closely associated with the two neuropathological biomarkers of Alzheimer's disease namely senile plaques (SPs) and neurofibrillary tangles (NFTs) [89]. Under fructose-induced hyperinsulinemic conditions, insulin competes with amyloid b protein (Aβ) for insulin-degrading enzyme, leading to the accumulation of Aβ and deposition of SPs [90]. In addition, the fructose-induced impairment of the insulin receptor (IR) signaling culminates in loss of insulin-mediated activation of phosphoinositide 3-kinase (PI3-K)/Akt pathway, and subsequent dephosphorylation of glycogen synthase kinase-3b (GSK-3b), which potentiates the phosphorylation and formation of NFTs [91]. The significant correlation between Akt activity/protein levels found in human Alzheimer's disease indicates a time-dependent and insulin-stimulated PI3-K signaling [92].

Experimental studies have demonstrated that fructose consumption aggravates the effects of brain trauma on molecular systems engaged in cell energy homeostasis (SIRT1, PGC-1α) and synaptic plasticity (BDNF, TrkB, CREB, synaptophysin) in the hippocampus. Fructose also aggravates the effects of brain trauma on spatial memory in association with a decrease in hippocampal insulin receptor signaling [73]. High fructose consumption under the threshold for establishment of MetS exacerbates the disruptive effects of brain trauma on inflammation and lipid peroxidation in the liver [22]. These effects seem to engage the neuroendocrine growth hormone system with increases of a metabolic/inflammatory cascade and lipid peroxidation, and disruption of cell energy homeostasis and insulin signaling. Diet-induced metabolic disorders pose a risk for incidence of post-stroke depression [93], and exacerbate damage caused by ischemic stroke in cerebral vessels [94]. These events result in an increase in BBB permeability and pro-inflammatory response that may exacerbate infarct volume [95,96].

9. How much and for how long fructose exposure can harm systemic physiology and brain function

The period of fructose exposure seems a critical factor for the involvement of systemic metabolism and subsequent effects on brain. A minimum of 6 weeks of fructose in rodents is crucial for development of MetS with concomitant effects on brain function and cognition [97,98]. Long-term high fructose consumption (15% solutions for 6 weeks) in rodents results in decrements in brain plasticity and learning and memory performance [69]. Fructose alters brain molecular pathways involved in mitochondrial bioenergetics and plasma membrane homeostasis, neuronal signaling, and synaptic plasticity [72]. Nevertheless, several studies indicate that a short period of fructose feeding for a duration insufficient to disrupt peripheral metabolism can also affect the brain by reducing cerebral blood flow [64], myelin basic protein, and the axonal growth-associated protein 43 (GAP-43), concomitant with a decline in hippocampal weight [99]. Two weeks fructose (20.4 g/100 g) diet induce inflammation, oxidative stress, impairment of insulin signaling as well as a significant decrease in mitochondrial function in the hippocampus [80]. Although the greater amount of fructose is intuitively worse for systemic physiology, information derived from animal studies is not conclusive since animals adjust their own fructose consumption based on caloric contents.

Although the BBB has low affinity for fructose [100], a short term (7 days) fructose consumption (20% solutions) seem to enable neuronal cells to metabolize fructose [101] as evidenced by increased levels of GLUT5 in hippocampal microglia [102] and cerebellar Purkinje cells [103]. Short fructose consumption also produces insulin signaling alterations accompanied by neurite and synaptic reduction and astroglial activation in the rat hippocampus [104]. Also, the hippocampus and hypothalamus [105] contains the enzyme Ketohexokinase (KHK) that degrades fructose reinforcing the possibility that fructose can be metabolized in the brain [106,107].

10. Concluding remarks and perspectives

Although fructose, as a natural component of fruits and honey, available to our ancestors for thousands of years of evolution, current overconsumption of dietary fructose is a major concern for public health. Studies indicate that several of the peripheral actions of fructose such as increased adiposity, triglycerides, and pro-inflammatory agents, can impact brain function. Current evidence indicates fructose disrupts function of several organs and systems that contribute to brain pathology. These actions of fructose can affect appetite, motivation and reward, and cognition by involving the hypothalamus and hippocampus. Excess dietary fructose fosters neurological and psychiatric disorders like anxiety, depression and Alzheimer's disease, in addition to brain trauma. Peripheral metabolism is a sensitive target to develop dietary management initiatives to reduce the silent epidemic of metabolic disorders that ultimately disrupts brain and body function.

Declaration of competing interest

The authors declare no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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