

Impact of sugar on the body, brain, and behavior

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Sugar on the body, brain, and behavior
 - 3.1 Fructose vs. glucose
 - 3.2 Hedonic response to sugar and rewards of sugar intake
 - 3.3 Hedonic response: fructose vs glucose
 - 3.4 Sugar addiction
 - 3.5 Sugar, obesity, and cognitive functioning
4. Sugar compared
 - 4.1. Sugar vs. fat
 - 4.2 Sugar vs. complex carbohydrates
5. Conclusions and future directions
6. Acknowledgement
7. References

1. ABSTRACT

Sugar is highly palatable and rewarding, both in its taste and nutritive input. Excessive sugar consumption, however, may trigger neuroadaptations in the reward system that decouple eating behavior from caloric needs and leads to compulsive overeating. Excessive sugar intake is in turn associated with adverse health conditions, including obesity, metabolic syndrome, and inflammatory diseases. This review aims to use recent evidence to connect sugar's impact on the body, brain, and behavior to elucidate how and why sugar consumption has been implicated in addictive behaviors and poor health outcomes.

2. INTRODUCTION

The past several years have been marked by a growing awareness of the unsavory effects of excessive sugar consumption. As of 2015, the World Health Organization recommends reducing added sugar to less than 5% of daily caloric intake to lower the risk of unhealthy weight gain and obesity (1). Last year, the American Academy of Pediatrics recommended that parents should not feed fruit juice to infants younger than one year because of its high sugar content (2). This advice reflects a growing body

of research investigating added sugar as an instigator of obesity and metabolic syndrome (a combination of risk factors like high blood pressure, high triglycerides, high fasting blood glucose, etc. that increase the likelihood of cardiovascular disease, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (3). Other research has examined sugar as a potentially addictive substance. However, the public is still flooded with mixed messages from advertising, health organizations, and popular press about sugar's impact on human health. Unbiased scientific findings from the past several years have begun to help clear up this consumer confusion.

Sugar typically refers to a category of simple carbohydrates that includes monosaccharides like fructose and glucose, and disaccharides, like sucrose and lactose, which have different effects on the body and brain. The present review focuses primarily on added sugars, namely sucrose and high fructose corn syrup (HFCS), because of their negative impact on health and because they predominate in the typical western diet. Sucrose, or table sugar, is a disaccharide made up of one-part glucose and one-part fructose. In contrast, HFCS is comprised of 42% or 55% of free

fructose, complemented by free glucose (4). Because most added sugar consumption comes from sucrose or HFCS, we typically consume both fructose and glucose together. However, research on the individual monosaccharides, fructose and glucose, has revealed large differences in how they affect the body.

The present review aims to explore sugar and its physiological effects on the brain and body, which may play a role in its adverse health effects. First, we discuss different types of sugar and how they are processed by the body and brain. Second, we address sugar's hedonic effects, addictive properties, and connections with obesity, primarily focusing on imaging studies in humans with support from the animal literature. Third, we aim to compare how sugar is metabolized and processed compared to other macronutrients such as fat and fiber-rich complex carbohydrates to further emphasize any singular effects attributable to sugar.

3. SUGAR ON THE BODY, BRAIN, AND BEHAVIOR

3.1 Fructose vs. glucose

Monosaccharides differ in how they are processed by the brain and influence brain activity. Although some consumers may believe that fructose is healthier because it comes from fruit (5), this notion is misguided. The body does not respond in the same way to fructose in fruit as to added fructose. As an added sugar, fructose is particularly implicated in metabolic syndrome, hypertension, insulin resistance, lipogenesis, diabetes and associated retinopathy, kidney disease, and inflammation (4,6,7,8,9). Accordingly, reduction of fructose in the diet of at risk individuals appears to reduce these symptoms. When added fructose was replaced by glucose (in the form of starch) in the diets of obese children, liver fat, de novo lipogenesis, diastolic blood pressure, triglycerides, and LDL cholesterol decreased while insulin sensitivity improved (10,11). Furthermore, in fruit, fructose is accompanied by antioxidants, flavonols, potassium, vitamin C and high fiber, which may collectively outweigh any negative consequences of fructose content (4, 12). Importantly, the quantities of fructose in a piece of fruit and a sweetened beverage are drastically different. For example, the fructose in a peach represents approximately 1% of the fruit's weight whereas fructose accounts for half the weight of HFCS (7).

Differences in health effects between glucose and fructose may be caused by the different metabolic pathways they follow. Digestion and absorption of sugars takes place in the top half of the digestive tract (13). Most of the glucose in the blood stream is not stored in the liver but rather, through the action of insulin, quickly passes through to muscle, adipose,

and other peripheral tissues where it can immediately be used as energy (13). Fructose, on the other hand, is a less direct source of energy. Independent of insulin, the liver converts fructose to glucose, lactate, and/or fatty acids before passing it to the blood stream where it can be oxidized in other tissues for energy (14,15,8). Compared to glucose, fructose produces smaller increases in plasma glucose and circulating satiety hormones such as glucagon-like peptide-1 (GLP-1) and insulin (16). Fructose also attenuates suppression of ghrelin, an appetitive hormone, while glucose does not (17). Therefore, fructose allows overconsumption of calories by failing to activate the body's signals to stop eating.

Beyond weight gain and obesity, other diseases are linked to fructose's metabolic pathway. High dietary fructose can increase de novo lipogenesis in the liver (18) in a way that is reminiscent of ethanol (19). This is because fructose bypasses the main rate limiting step of glycolysis to act as a precursor for fatty acid synthesis (20,21,8). This bypass may also explain the increased rates of non-alcoholic fatty liver disease and resulting insulin resistance associated with fructose ingestion (20). Fructose also seems to contribute to inflammation in the body. When in excess in the intestinal lumen, fructose generates advanced glycation end products (AGE's), which are related to neurodegenerative diseases, atherosclerosis, and chronic inflammatory diseases such as asthma, diabetes, and associated cognitive decline (22,9,23,24,25).

Glucose and fructose have differing impacts on the brain. Compared to other organs, the brain has vastly disproportionate energy requirements relative to its weight. Neurons have an especially high energy demand for generating postsynaptic potentials and action potentials, necessitating large amounts of energy (26). Glucose from the bloodstream is the main source of energy for the brain (26,27). Glucose transporters in astrocytes and the epithelial cells of the blood brain barrier (BBB) are responsible for transporting glucose into the brain (16,26). Neurons then absorb glucose from astrocytes using glucose transporters. In contrast, fructose cannot directly supply the brain with energy as it crosses the blood brain barrier to a much lesser degree than glucose (16,26). However, fructose administered intraperitoneally in rodents crossed the BBB to some degree and triggered neuronal activation. This fructose was metabolized into lactate, an alternate energy source, in the hypothalamus (16). Fructose's ability to cross the BBB has not yet been studied in humans, so more research is needed on the direct effects of fructose in the brain. Nonetheless, the differential effects of the two monosaccharides may be attributed in part to glucose's more immediate and direct availability to the brain as an energy source as compared to fructose.

3.2 Hedonic response to sugar and rewards of sugar intake

While the hypothalamus regulates food intake in terms of energetic needs, the dopamine reward/motivation circuitry involving striatal, limbic and cortical areas also drives eating behavior (28). Other neurotransmitters including serotonin, endogenous opioids, and endocannabinoids confer the rewarding effects of food in part by modulating its hedonic properties (29). Ingestion of palatable food releases dopamine (DA) in the ventral and dorsal striatum and dorsal striatal DA release is proportional to the self-reported level of pleasure gained by eating the food (30). Highly palatable foods, namely those rich in sugar or fat, can strongly trigger these reward/motivation and hedonic systems, encouraging food intake beyond the necessary energy requirements (31). While this may have been evolutionarily advantageous by encouraging fat storage when food was scarce, overeating becomes a liability in our current environment, which has no shortage of highly caloric and processed foods.

There are two principal rewarding aspects of sugar consumption: nutrition and taste. Rodent studies have indicated that these two aspects are distinct and dissociable and may follow different neural pathways (32,33). One path for the nutritive rewards of sugar comes from melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus (32). In rodents, these neurons fire in response to extracellular glucose levels, independent of gustatory input, and project to dopamine neurons in the midbrain that in turn project to the ventral and dorsal striatum. Though animals typically prefer sucrose over sucralose (non-nutritive sweetener), transgenic mice who lack MCH neurons do not, showing that this pathway is essential for encoding nutritive reward. When MCH neurons are optogenetically stimulated during the consumption of sucralose, the mouse brain is tricked into responding as if it is receiving caloric energy with a resultant increase in striatal DA and even preference of sucralose over sucrose (32). The nutritive reward value of sugar is associated with increases in DA release in the dorsal striatum (34). When infused intra-gastrically in mice to avoid the confounds of taste, glucose elicited DA release in the dorsal striatum while sucralose did not (34).

The sweet taste of sugar is also rewarding—offering an explanation as to why artificial sugars like sucralose are still consumed despite their lack of nutritive value. The reward of the sweet taste, however, activates a different neural pathway than the caloric input. While the nutritive reward of sugar in mice causes DA release primarily in the dorsal striatum, the sweetness reward is concentrated in the ventral striatum (32). Consumption of sucralose in mice was associated with increased DA in the ventral striatum except when tainted by a bitter additive, suggesting

that the reward is derived from the palatable taste rather than another feature of sucralose (34).

Although both the nutritive and taste rewards of sugar are, to some extent, neurologically distinct, they occur in tandem and are interrelated. A recent study showed that mice modified to have disrupted DA D-2 receptor (DRD2) signaling in the nucleus accumbens (NAc) shell of the ventral striatum exhibited more perseverative and impulsive sucrose-taking, increased sucrose reinforcement, increased reinforcement/reward learning of glucose-paired flavors, and worsened learning flexibility (35). Additionally, these mice were less efficient in metabolizing glucose. This suggests that DRD2 in the NAc are essential both for regulating peripheral glucose levels as well as the reinforcement/reward learning of glucose consumption (35), which explains why dysregulation of this system may lead to overeating.

3.3 Hedonic response: Fructose vs. glucose

Just as fructose and glucose have different metabolic pathways, they have different hedonic effects on the brain and behavior. Fifteen minutes after subjects received a drink of either pure fructose or glucose during a functional MRI (fMRI) scan, those receiving glucose showed a significantly reduced amount of cerebral blood flow (CBF) in the hypothalamus, insula, anterior cingulate cortex, and striatum when compared to baseline (17). They also showed greater functional connectivity between the hypothalamus, thalamus, caudate, and putamen. The increased connectivity between the hypothalamus and the dorsal striatum after glucose was interpreted to reflect engagement of the nutritive reward pathway. The reduction in hypothalamic activity and increased connectivity with reward centers was accompanied by a perceived increase in fullness and satiety. In contrast, consuming a fructose drink was not associated with reduced CBF in the hypothalamus, but instead with reduced CBF in the thalamus, hippocampus, posterior cingulate cortex, fusiform gyrus, and visual cortex. Although those in the fructose group did have increased connectivity between the thalamus and hypothalamus, there was no increase detected with the dorsal striatum as observed in the glucose group. Correspondingly, fructose consumption did not significantly reduce hunger. Fructose consumption has also been associated with a stronger fMRI response in the visual cortex to high calorie foods compared that with glucose consumption (14). As fructose delivers a sweet taste without an immediate nutritive input, it follows that fructose consumption should be associated with increased appetitive behavior and reactivity to food.

3.4 Sugar and addiction

Sugar has been characterized by some as an addictive substance, with properties comparable to

that of drugs of abuse. Nonetheless, explicit evidence of pure sugar addiction has thus far been limited to research with rodents. Rat studies have shown that sugar addiction may be induced by intermittent access to sugar and in many ways resembles opiate addiction (36). Rats with 12-hour access to sugar followed by 12 hours of food deprivation showed "bingeing", "withdrawal", "craving", and cross sensitization to drugs of abuse, like amphetamine¹ (37,38). When these sugar exposed mice were given naloxone, an opioid antagonist, they showed withdrawal symptoms as observed with mice chronically exposed to opioid drugs (39,36,40). Because the same reward-related brain structures (i.e., NAc shell, caudate nucleus), respond to the positive valence and saliency of both sugar and drugs, there is reason to believe that their mechanisms of producing addictive behavior as well as physical and psychological responses are related (41,42,43,44). In fact, using a free-choice lever pressing paradigm, Lenoir and colleagues showed that rats find high levels of sweetness from non-nutritive saccharin or sucrose more rewarding than cocaine even for rats that were already dependent on cocaine (45).

Like other rewarding stimuli, intake of sucrose induces DA release in the NAc, but after repeated exposure and conditioning, DA efflux is more prominent in dorsal striatal areas, which are important for habitual behaviors (46,47). Parallel to changes seen in opiate addiction, sugar addiction in rats is marked by an upregulation of dopamine D1 and mu-1 opioid receptors in the NAc shell, and a decrease of DRD2 in the striatum (48,49,50). However, this effect is much more pronounced in the NAc of sugar-taking rats while more evenly distributed across the dorsal and ventral striatum for morphine-exposed rats (50). Still, deep-brain stimulation in the NAc shell prevented relapse of both cue-induced sugar and cocaine consumption in rats (51).

Evidence of similar predispositions for sugar and drug-taking further highlight their shared mechanisms. Alcohol and drug abusers tend to have a greater preference for sweet foods, especially those with a family history of alcoholism or drug addiction, suggesting a genetic component to this association (52,53). A recent study exploring the heritability of high sugar consumption and substance use disorders (SUDs) found that these two phenomena were correlated, and that both genetic and environmental factors (59% and 41% correspondingly) explained the variability in the relationship (54).

3.5 Sugar, obesity, and cognitive functioning

Some scientists argue that the obese brain is addicted to food, particularly highly processed food containing added sugar or fat. In both rodents and humans, lower DRD2 in the striatum is seen in obesity

as in drug addiction (55,56). However, others argue that only the subset of obesity corresponding to binge eating disorder (BED) involves food addiction (57). Cravings for sweets and carbohydrates can partially mediate the significant association between addictive-like eating symptoms and binge eating episodes (58). As cravings are a core feature of addiction, this is a necessary component to implicate sugar as a potentially addictive substance.

The typical pattern of response to glucose and fructose is somewhat altered in obese individuals. Compared to lean adolescents, obese adolescents showed reduced perfusion in the prefrontal cortex (PFC) and increased perfusion in the hypothalamus and striatum following a glucose drink (59). In the fructose drink condition, obese adolescents once again had reduced CBF in the PFC and increased CBF in the striatum, especially the NAc, while lean adolescents did not (59). There also appears to be evidence of insufficient down regulation of appetite following caloric intake in adult obese individuals. Using positron emission tomography (PET) with (¹¹C)raclopride to measure DA release and DRD2 occupancy in the striatum, Wang and colleagues showed that obese individuals had a reduced DA response in the ventral striatum after consuming a glucose drink (controlling for sweet taste with a sucralose condition) compared to lean participants (60, Figure 1). Because DRD2 mediates the inhibition of aversive responses, i.e. hunger, the reduced DA release with caloric consumption in obese individuals might contribute to excess food intake.

Added sugar consumption has also been associated with cognitive impairments, especially worsened hippocampal memory function. Rats on a high sugar/low fat, or a high sugar/high fat diet show hippocampal-dependent memory deficits (61). This relation appears to be mediated by increased hippocampal inflammation, which is especially pronounced in the high sugar/low fat condition (61). Associations in humans support these findings: greater relative carbohydrate intake predicted a heightened risk of mild cognitive impairment or dementia in elderly people, while carbohydrate intake in school children was negatively associated with nonverbal intelligence tests (61).

In contrast, the ketogenic diet (KD), a high-fat, low-protein and low-carbohydrate diet (e.g., a 4:1 or 3:1 ratio of fat to carbs and protein), has gained traction to manage different neurological and psychiatric disorders and promote weight loss. This diet induces a state of ketosis so that the brain uses ketone bodies for energy rather than glucose. The diet has shown consistent clinical benefit in patients with epilepsy, possibly due to the increase of acetone in the brain, which has anticonvulsant effects (62,63,64,65,66).

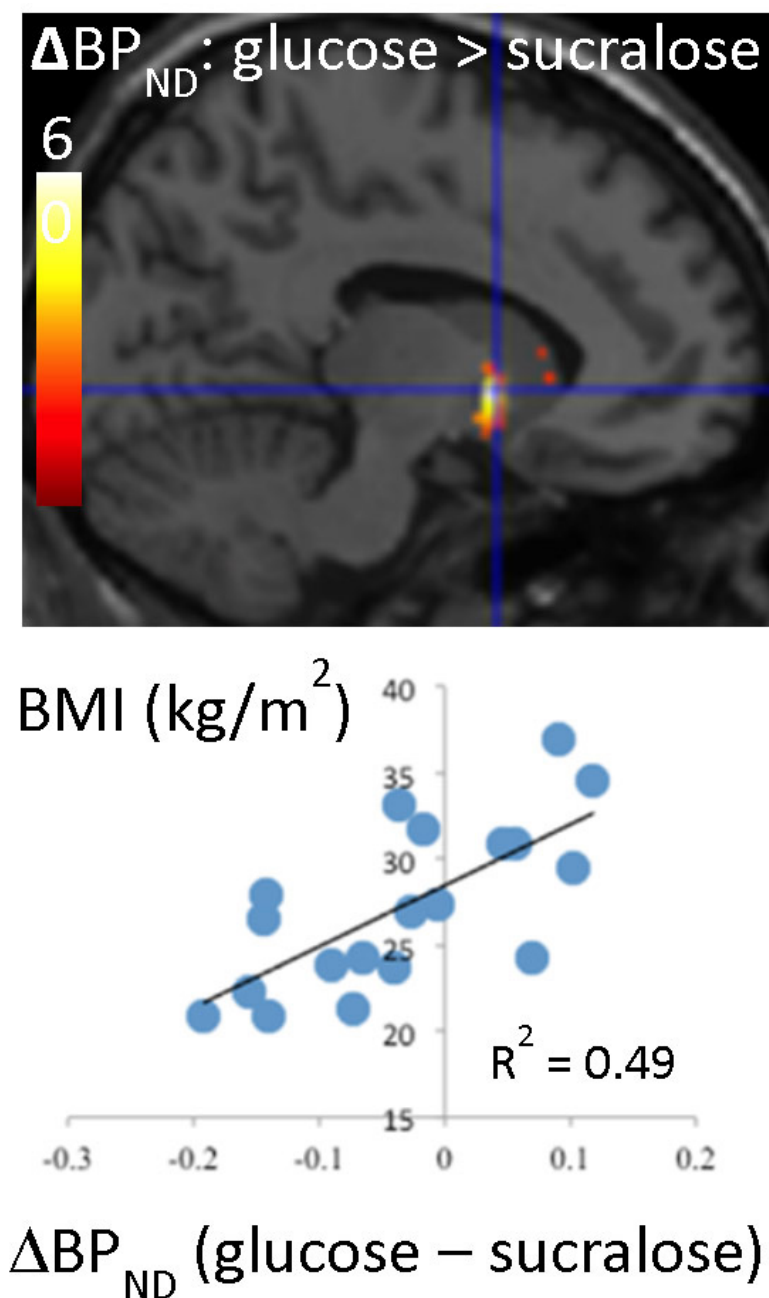


Figure 1. Top: Statistical significance of dopamine (DA) changes in nucleus accumbens for the contrast glucose > sucralose intake (ΔBP_{ND}). Bottom: Correlation between BMI and brain DA changes. Reproduced with permission from (60).

Other less studied neurological conditions in which KD has been used are Alzheimer's Disease, where daily use of a ketogenic compound lead to cognitive improvements 45-90 days later (67), and Parkinson Disease (68). The effects of KD have also been studied in psychiatric disorders including ADHD, depression, autism, anxiety, bipolar disorder, and schizophrenia, but there is currently insufficient evidence available as to whether the diet shows clinical efficacy (69). Further research is needed to establish how the benefits of the

ketogenic diet may be related to the detrimental effects of high sugar consumption.

4. SUGAR COMPARED

4.1 Sugar vs. fat

Sugar consumption alone will not lead to weight gain or obesity--even rats exhibiting addictive behavior towards sugar do not gain weight (70,71).

The same is true for fat--rats given intermittent access to fat will binge on it, but will not gain significant weight (70). However, like sugar, fat also increases food palatability, which can lead to hyperphagia. Higher fat content in food is a large, significant predictor of problematic, addictive-like eating in humans (71). Lower DRD2 may be a risk factor not only for compulsive sugar-taking but also for fat bingeing; rats with knocked down DRD2 exhibited more compulsive eating of highly palatable fat-rich foods (72). Further, it appears that greater amounts of fat may increase the likelihood that a food will be consumed problematically, even in those who do not report consuming food in an addictive-like way (73).

While fat or sugar alone may not induce weight gain, together they do. Highly processed foods, which are often over-consumed, tend to contain both fat and added sugar (e.g. ice cream, pizza, etc). Sugar-coating of fatty foods can further increase their palatability, contributing to overeating and weight gain. Therefore, sugar and fat eaten together is a very potent combination with implications for obesity. Interestingly, rats who binged on a fat-sweet diet gained weight but did not display the same withdrawal effects as the sugar-addicted rats (70). Fat intake may protect against opiate-like withdrawal symptoms associated with excessive sugar consumption, despite the other problematic health effects of the sugar/fat combination.

4.2 Sugar vs. complex carbohydrates

Irrespective of sugar, not all carbohydrates are associated with adverse health effects. While some complex carbohydrates, like starches, are broken down into monosaccharides, others, like the ones found in fruits, vegetables, and fiber-rich whole grains and legumes, follow a different metabolic pathway. Unlike sugars, which can be absorbed in the upper half of the GI tract, certain complex carbohydrates are not digestible by human enzymes and must be broken down by microbes in the large intestine (74,13,75,76,77). Gut microbes produce short chain fatty acids (SCFAs) as a byproduct of the fermentation of these complex carbohydrates. The primary SCFAs produced are acetate, propionate, and butyrate, which can be used by the body as an energy source. Complex carbohydrates are more filling than sugars because SCFAs can increase the release of hormones and peptides from enteroendocrine cells that result in increased satiety, thus reducing food seeking behavior (78).

In direct contrast to the effects of excessive sugar intake, especially fructose, SCFAs seem to have multiple health benefits including anti-inflammatory effects, antidiabetic effects via suppression of insulin signaling, inhibition of fat storage, and decreased body

fat and weight (79,75,13,76). As previously mentioned, sugar ingestion seems to increase the inflammatory response in the body. Excessive sugar intake has been associated with an increase in diabetes and associated cognitive impairment mediated by an increase in inflammation (23). Diabetes also involves the impairment of insulin signaling along with the presence of low-grade inflammation (23). These aspects of the pathogenesis of diabetes seem to parallel the effects of fructose on the body (20). Fructose metabolism may cause inflammation by increasing fatty acid oxidation in the liver and increasing transcription of inflammatory factors (7,8). Therefore, the SCFAs produced by gut microbes in the digestion of complex carbohydrates could be a source of protection against the inflammatory effects of a high fructose diet.

The anti-inflammatory effects of SCFAs are also seen in the brain. Gut microbes seem to regulate the central nervous system via pathways involving the immune system and the vagus nerve (78,76). SCFAs can elicit cell signaling by binding to G-protein receptors found in multiple locations, including nerve fibers of the portal vein, enteroendocrine cells of the intestines, glial cells in the brain, and adipocytes. This binding seems to suppress a neuroinflammatory response: butyrate treatment has been shown to protect against lipopolysaccharide (LPS) inflammatory responses in microglia. Despite these findings of indirect anti-inflammatory effects, propionate has been shown to promote microglial activation (78) and the full effects of complex carbohydrate metabolism on the brain are still unclear. Future research is necessary to determine whether SCFAs cross the blood brain barrier to have a more direct effect on the brain and behavior, including how they might counterbalance the effects of sugar and food-seeking.

5. CONCLUSIONS AND FUTURE DIRECTIONS

Sugar is a highly palatable food that triggers our reward systems due to both caloric input and taste. Taken in excess, sugar can trigger these reward systems too strongly, inducing compulsive eating. The nutritive and taste reward centered in the striatum and the homeostatic signaling from the hypothalamus become less effective at communicating with each other to signal satiety. Added fructose is especially disruptive because it is not immediately available as an energy source for the brain, providing a sweet taste without the accompanying beneficial and timely nutritive input. The following dysregulation of eating behavior in many ways parallels the compulsive consumption of drugs in addiction.

When we examine glucose and fructose separately, added fructose is associated with many more health risks than glucose. Fructose can increase food-seeking and lead to fat production and

storage. It may also be related to neurodegenerative inflammatory disease like diabetes and Alzheimer's. As an alternative to sugar, complex carbohydrates in fruits, vegetables, legumes and fiber-rich grains are fermented by gut microbes, producing SCFAs, which may counterbalance the inflammatory effects of sugar.

The evidence of sugar addiction in rat models does not clearly translate to humans. Because fat seems to protect against sugar withdrawal symptoms in rats, we may be unable to identify pure sugar withdrawal in humans due to our naturally varied diet. Nonetheless, overlap between the risk factors, neurobiological substrates, and behavioral effects of drug addiction and sugar bingeing suggest that added sugar is a problematic substance that might trigger behaviors akin to those of addictive drugs. The combination of sugar and fat is especially potent for triggering food overconsumption and weight gain. While each alone will not cause weight gain, sugar and fat together are highly palatable and can induce weight gain and obesity.

Although it is clear that excess added sugar, fructose in particular, has adverse health effects, further research is needed to study the mechanisms of these effects, including how sugar affects the brain. One particularly pressing line of research is to understand the direct effects of fructose and SFCAs on the brain. Although there is preliminary evidence that SFCAs may counter the inflammatory effects of fructose, we still do not know to what extent they are able to cross the blood brain barrier and how they are processed in the brain. This research may have important implications for type 2 diabetes, which has been associated with dementia and cognitive impairment, as well as for Alzheimer's and other diseases (23).

Another future direction of clinical concern is research trials on dietary interventions for neurological and psychiatric health, as recent studies increasingly show adverse effects of dietary sugar on mental health problems, such as ADHD (80), and sleep duration (81). More randomized controlled trials on the effects of the ketogenic diet and similar diets in psychiatric disorders are needed.

In summary, reducing added sugar consumption may help to promote healthy eating behavior and maintain overall physical and behavioral health. Future research in the form of RCTs is needed in humans to fully understand the systems-wide effects of sugar.

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Note: ¹ Interestingly, rats with 24-hour access to sugar do not become addicted, perhaps because free-access prevents the cycle of bingeing, withdrawal, and craving (Avena, 2008).

Key Words: Sugar, Addiction, Brain, Eating Behavior, Review

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