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Attention-Deficit/Hyperactivity Disorder: Is it Time to Reappraise the Role of Sugar Consumption?

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) affects nearly 10% of children in the United States, and the prevalence of this disorder has increased steadily over the past decades. The cause of ADHD is unknown, although recent studies suggest that it may be associated with a disruption in dopamine signaling whereby dopamine D_2 receptors are reduced in reward-related brain regions. This same pattern of reduced dopamine-mediated signaling is observed in various reward-deficiency syndromes associated with food or drug addiction, as well as in obesity. While genetic mechanisms are likely contributory to cases of ADHD, the marked frequency of the disorder suggests that other factors are involved in the etiology. In this article, we revisit the hypothesis that excessive sugar intake may have an underlying role in ADHD. We review preclinical and clinical data suggesting overlaps among ADHD, sugar and drug addiction, and obesity. Further, we present the hypothesis that the chronic effects of excessive sugar intake may lead to alterations in mesolimbic dopamine signaling, which could contribute to the symptoms associated with ADHD. We recommend further studies to investigate the possible relationship between chronic sugar intake and ADHD.

Keywords

ADHD; sucrose; fructose; high-fructose corn syrup; reward-deficiency syndrome; dopamine; D_2 receptor; obesity

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Introduction

The Centers for Disease Control and Prevention recently reported that nearly 1 in 10 children in the United States aged 4 to 17 years have parent-diagnosed attention-deficit/ hyperactivity disorder (ADHD), representing 5.4 million children, half of whom are actively receiving medication.[1] Attention-deficit/hyperactivity disorder is diagnosed by specific criteria (such as the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [DSM-IV-TR]),[2] including hyperactivity and inattention, an inability to focus, becoming distracted easily, and making careless errors. Other features include impulsiveness, emotional lability, fidgeting, and excessive talking.[3,4] Attention-deficit/hyperactivity disorder is commonly associated with learning disorders and impaired school performance; it may also affect socialization and have psychiatric manifestations (eg, mood disorders, conduct disorders, and bipolar manifestations).[5] Furthermore, manifestations of ADHD commonly continue into adulthood,[3] affecting 3% to 5% of the adult population.[6] Adults with ADHD, compared with adults without ADHD, have an increased risk for substance abuse (16% vs 4%, respectively) and antisocial behavior (18% vs 2%, respectively).[7] Treatment consists of behavior-modification programs and pharmacotherapy with stimulant drugs (eg, amphetamine or methylphenidate) that increase extracellular levels of both dopamine and norepinephrine, or the selective norepinephrine reuptake inhibitor atomoxetine.[8] While these treatment approaches often improve symptoms, complete resolution of symptoms is rare and cure is infrequent.[3,5,9]

Identifying the etiology of ADHD is paramount for developing better ways to prevent and treat the disorder. A number of studies suggest that ADHD may have a genetic basis, and there is increasing evidence to suggest that this may relate to polymorphisms in genes involved in dopamine neurotransmission.[10] Indeed, there is increasing evidence to suggest that ADHD may involve alterations in mesolimbic dopamine signaling (Figure 1). For example, the polymorphism *DRD2-TAQ-IA*, which results in low striatal D_2 receptors, also results in increased risk for alcohol and opioid addiction,[11] obesity,[12,13] and ADHD.[14–16] Nevertheless, while the importance of genetics in ADHD is not disputed, the few genetic linkages identified to date can account for only a small percentage of ADHD cases.[10] Thus, it is important for us to consider other possible factors that might cause or predispose individuals to develop ADHD.

One theory among lay people is that sugar consumption may have a role in ADHD, and parents are often of the opinion that acute ingestion of sugar may cause bouts of hyperactivity in their children, followed by sedation and inactivity.[17] Nevertheless, studies performed in the 1980s appeared to rule out sugar as a likely cause of ADHD. However, while prior studies on sucrose intake and ADHD were outstanding in design, they evaluated the acute effects of sugar on symptoms of ADHD and also mostly compared the effects of sucrose with the effects of non-nutritive sweet tastes. In contrast, because ADHD is a chronic disorder, we present the hypothesis that the chronic effects of excessive sugar intake could be a mechanism associated with ADHD. We further hypothesize that sweet taste (provided by sugar or artificial sweeteners) is sufficient to affect the mesolimbic dopamine system in a way that could result in behaviors common to ADHD.

Early Studies of Sugar and ADHD

Some early studies supported the concept that increased intake of added sugars may have a role in ADHD. For example, a study by Prinz et al[18] reported that hyperactive children who ingested more sucrose showed greater hyperactivity. However, elegant studies led by Wolraich and others provided convincing evidence that sugar (sucrose) intake is not related to symptoms of ADHD.[17,19–22] For example, the administration of sugar for 3 weeks was no

different from the administration of aspartame or saccharine in inducing signs of ADHD in children thought to be sensitive to sucrose.[20] In another study, children with "sugar sensitivity" were rated for hyperactivity by parents who were told that their children were administered aspartame or sucrose. The parents rated children who received sucrose as having worse behavior; however, in actuality, both groups received aspartame.[22] In another study, the administration of sucrose resulted in similar behavior as the administration of aspartame in hyperactive boys.[19] The inability to document an effect of added sugars on hyperactivity, even in children thought to be sensitive to the stimulatory effects of sugar (mostly when compared with other sweet tastes, such as aspartame), has largely discredited the sugar hypothesis of ADHD. Indeed, a meta-analysis of clinical trials conducted 15 years ago concluded that sugar is not the cause of ADHD.[21]

Hypothesis: Chronic Sugar Intake May Cause Symptoms of ADHD

Our basic hypothesis is shown in Figure 2. In essence, we suggest that in some subjects, the initiating process that leads to the development of ADHD is excessive sugar (or sweetener) intake, resulting in enhanced dopamine release. Over weeks to months, this leads to a reduction in D_2 receptors and D_2 receptor-mediated signaling. In response, sugar intake increases. However, over time, the dopamine response to sugar slowly decreases, and the intervening periods are associated with a reduction in striatal dopamine levels. As a consequence, frontal lobe sensitivity to natural rewards is reduced, resulting in the development of behaviors such as overeating and ADHD.

Chronic Sugar Intake and ADHD Show Changes in Dopamine and D_2 Receptor Signaling, Similar to Drug Addiction

Recurrent stimulation of dopamine in the ventral striatum (nucleus accumbens) and dorsal striatum (caudate/putamen) by drugs such as cocaine or heroin can lead to addiction-like behaviors.[23,24] Although signaling via both D_1 and D_2 receptor subtypes is involved in addiction, most human studies are based on analysis of D_2 receptors, as they correlate with features of addiction and can be quantified using positron emission tomography (PET) scanning with raclopride C11 ([^{11}C]raclopride), which binds selectively to D_2 receptors.[25] Such studies have shown that D_2 receptors are reduced in reward-related brain regions in cocaine and heroin addicts.[25,26] A reduced number of nucleus accumbens D_2 receptors prior to drug exposure also predicts cocaine self-administration in rats.[27] Collectively, these studies suggest that recurrent release of dopamine may result in a downregulation of striatal D_2 receptors, predisposing that individual to the development of drug addiction. The concept that fewer D_2 receptors may increase vulnerability to addiction is also supported by the finding that subjects with the *DRD2-TAQ-IA* polymorphism have reduced D_2 receptor density and are at increased risk for alcohol and opiate addiction.[11]

The mechanism by which low striatal D_2 receptors leads to addictive behavior may relate to the known relationship between dopamine signaling and cortical control mechanisms. The dorsolateral prefrontal cortex and medial prefrontal cortex are involved in controlling behavior and motivation, and are altered in subjects with drug addiction.[28] The observation that subjects with low D_2 receptors due to polymorphisms in *DRD2-TAQ-IA* have altered prefrontal lobe metabolism and show a learning disability with the inability to avoid actions with negative consequences also supports a role for a causal connection between D_2 receptor density and cortical control behavioral mechanisms.[12] The additional observation that morbidly obese subjects also show altered prefrontal metabolism that correlates with low D_2 receptors and addictive behaviors further supports this important link.[29]

Sucrose is a potent stimulus for dopamine release. In rats, the ingestion of sucrose results in an immediate increase in extracellular dopamine in the nucleus accumbens,[30,31] and both sucrose intake and extracellular dopamine are enhanced if presynaptic reuptake of dopamine is blocked.[32] The increase in dopamine may increase behavioral responses that can lead to further ingestion of sucrose. For example, mice with genetically high dopamine levels show enhanced incentive performance for sucrose, increase their food and water intake, learn quicker, resist distractions, and proceed more efficiently to their goals.[33] While they have a greater "desire" response to sucrose, they do not appear to have a better liking (satisfaction) response to the sucrose.[33]

Although the acute effects of dopamine may enhance performance, the issue is whether desensitization of dopamine-stimulated responses occurs with repeated sugar administration. Much of our knowledge about the effects of sucrose on addiction-like behaviors in laboratory rats has come from studies by the laboratory of the late Bart Hoebel at Princeton University (Princeton, NJ), who developed a model of sugar overeating in rats by limiting their daily exposure to sucrose.[34] Specifically, rats offered sucrose 12 h/day for approximately 3 weeks escalated their daily intake of sucrose and binge ate sucrose on daily access. In these rats, administration of naloxone (an opioid antagonist) resulted in signs of opiate-like withdrawal (eg, teeth chattering, head shakes, and forepaw tremor) and signs of anxiety.[35] Signs of withdrawal are also observed if the sucrose and food are withheld.[36] Also, rats that have a history of bingeing on sucrose show a heightened sensitivity to drugs of abuse.[37,38] Thus, repeated intermittent sugar exposure may lead to a "sugar addiction" that involves behaviors similar to those seen with classical drug addiction.[34,39]

The effect of intermittent sugar consumption on nucleus accumbens dopamine release differs from what normally occurs in response to ingestion of a palatable food. While palatable foods release dopamine, this effect is more closely associated with the novelty of the food, and the release of dopamine attenuates with subsequent exposure to the food.[40] However, when rats repeatedly overeat sugar (ie, on a daily basis for 1 month), they continue to release dopamine from the nucleus accumbens on ingesting[30] or tasting[41] sucrose. Nevertheless, the observation that the dopamine response remains similar over time despite progressively higher intakes of sucrose suggests some desensitization.

Consistent with desensitization, chronic sucrose intake in rats is associated with a reduction in nucleus accumbens D_2 receptor mRNA expression compared with control rats.[42] There is also decreased D_2 receptor binding in this region,[43] a finding that has also been seen in a more restrictive intermittent sucrose exposure paradigm.[44] Striatal D_2 receptors are also reduced in rats consuming a sucrose-containing, cafeteria-style diet for 40 days, and these rats progressively increased their food intake and developed obesity.[45] These rats exhibited a higher reward threshold in response to electrical stimulation of the nucleus accumbens, suggesting that they might need to eat more of the sucrose-rich diet to achieve a comparable reward. In addition, these rats became progressively resistant to punishment (foot shock) paired with eating.[45] These effects were amplified by knocking down the striatal D_2 receptors in rats on the sucrose-rich diet.[45] Collectively, these studies suggest that repeated exposure to sugar may affect the mesolimbic dopaminergic response to palatable food, possibly due, in part, to lower D_2 receptors.

Brain dopamine signaling is also altered in patients with ADHD. Adults with ADHD show fewer D_2-like receptors in the left ventral striatum (involved in reward behavior), left midbrain, and left hypothalamus (involved in memory) compared with healthy adults, and the reduction in D_2 receptors correlated with degree of inattention.[46] Furthermore, there is reduced glucose metabolism in the prefrontal cortex of adults with ADHD, consistent with a loss of frontal control mechanisms.[47] Finally, there is also a reduction in dopamine

metabolites in cerebral spinal fluid samples obtained from children with ADHD.[48] Thus, ADHD has a similar dopamine biosignature as that observed with sucrose or drug addiction, with both showing a downregulation of striatal D_2 receptors. Attention-deficit/hyperactivity disorder is also associated with a reduction in frontal lobe sensitivity to natural rewards and greater symptoms of inattention,[46] and although this has not been shown in animals chronically fed sucrose, the observation that a genetic reduction in striatal D_2 receptors is associated with altered frontal lobe behavioral mechanisms[12] suggests that chronic sugar ingestion may have similar effects. The general link between dopamine D_2 receptors and frontal lobe control mechanisms has led Volkow et al[46] to propose that recurrent stimulation of dopamine release may lead to desensitization of the postsynaptic dopamine signaling pathways, which, in turn, reduces inhibitory signals generated by the frontal cortex, resulting in impulsive behavior and loss of emotional control, and symptoms of ADHD. Our contribution is primarily to suggest that this link may be due to chronic sugar intake. If true, chronic sugar intake should correlate with an increased prevalence of ADHD.

The Prevalence of Chronic Sugar Intake and ADHD Have Increased in Parallel

Sugar intake and ADHD have increased in parallel in recent years. The intake of added sugars in the United Kingdom and United States has increased remarkably over the past 2 centuries, with a marked acceleration in the past 40 years in association with the introduction of high-fructose corn syrup (HFCS).[49,50] Today, intake of added sugars accounts for 15% to 20% of daily caloric intake in adults; in 10% of adults and in 25% of children, the intake of added sugars may be > 25% of their diets.[51–53]

The prevalence of ADHD is difficult to assess, as definitions have varied over the years and because there are few large-population studies. However, studies published in the early 20th century on childhood psychiatric disorders focused on aphasia, dyslexia, and autism.[54] Reports of the hyperkinetic child or of abnormal fatigue in children are relatively limited through the first half of the 20th century.[55,56] Beginning in the late 1960s and 1970s, one can observe a dramatic increase in publications on children with ADHD, which at this time was termed "minimal brain dysfunction."[4] Estimates from as recent as 1990 suggested that approximately 2% to 5% of US school children have hyperactivity syndrome.[47,57,58] More recently, the National Survey of Children's Health consisted of a randomized, national, and cross-sectional survey of > 70 000 households with children between the ages of 4 and 17 years, which was conducted in both 2003 and 2007. These data show a > 20% increase in parent-reported ADHD between 2003 and 2007, increasing from 7.8% to 9.5% of children (consisting of an increase from 11.0% to 13.2% in boys and 4.4% to 5.6% in girls).[1] The National Health Interview Survey also reported an increase in ADHD between 1997 and 2006 at a rate of 3% per year.[59]

The increasing prevalence of ADHD is compatible with the known increases in sugar consumption in the United States. Although, to our knowledge, no studies have directly assessed whether a correlation exists between the prevalence of ADHD and sugar intake, there are a few reports linking ADHD with sugar consumption. Parents of children with ADHD report sleep disturbances that are associated with increased sugar intake.[60] Further, preschool-aged children who consumed a diet rich in "junk food" with a high sugar content were more likely to exhibit hyperactivity at age 7 years compared with children who ate less junk food.[61]

Chronic Sugar Intake and ADHD Are Both Associated with Obesity

The marked increase in sugar intake has been epidemiologically and physiologically linked with the increase in obesity and metabolic syndrome.[49,62] Attention-deficit/hyperactivity disorder is also associated with obesity.[63,64] In 1 study of children with ADHD aged 3 to 18 years, 29% had a body mass index (BMI) >85th percentile, which is twice the frequency observed in the normal population.[65] Another study found that nearly 20% of 5- to 14-year-old boys with ADHD had a BMI > 90th percentile.[65] In a study of Chinese teenagers (aged 13–17 years) with ADHD, the frequency of obesity was 1.4-fold greater than the frequency of being lean.[66]

Adults with ADHD are also commonly obese. In one study of adults with ADHD, the likelihood of being overweight was 1.58 (odds ratio [OR], 1.58; 95% confidence interval [CI], 1.05, 2.38) and for obesity the OR was 1.81 (95% CI, 1.14, 2.64).[6] Another study found that ADHD and hyperactivity were associated with both obesity and hypertension in young adults.[67] Conversely, obese subjects are also at increased risk for ADHD. Among children hospitalized for obesity, ADHD was diagnosed in > 50% of cases.[68] Further, in obese adults undergoing bariatric surgery, ADHD has been found in 27% of patients, and the frequency was even higher (42%) in those with morbid obesity (BMI > 40 kg/m^2).[69]

There are several potential explanations for the association between ADHD and obesity. First, characteristics associated with ADHD, such as depression or binge eating, may result in obesity.[6,63] The converse may also be true, that the presence of ADHD may interfere with the ability to lose weight via diet programs or following bariatric surgery.[69] A final explanation, which we are proposing in this article, could be that sugar intake may be driving both ADHD and the risk for obesity. Davis[63] also recently implicated dietary intake of fats and sugars in the pathogenesis of ADHD, particularly if ingested during pregnancy (which she described as a fetal sugar spectrum disorder).

Obesity Has a Dopamine Biosignature Similar to That of ADHD and Chronic Sucrose Ingestion

Striatal D_2 receptor availability is chronically decreased in obese subjects as determined by PET scanning with [^{11}C]raclopride.[70] Obese subjects also have fewer striatal D_2 receptors, which correlates with reduced glucose metabolism in the frontal and somatosensory cortices.[29] Obese individuals also have a reduction in dorsal striatal response, measured by functional magnetic resonance imaging (fMRI), to palatable food intake, consistent with a lower dopamine response and/or lower D_2 receptors.[71] Thus, obese individuals may overeat to compensate for impaired reward responses. While obese individuals typically show a reduced dopaminergic response to the intake of palatable food, they may show an enhanced response to the sight of food.[71] Binding of [^{11}C]raclopride to D_2 receptors decreases in the dorsal striatum when subjects who are pretreated with methylphenidate see appetizing food, and this expressed desire for food is consistent with an acute release of dopamine and occupation (stimulation) of D_2 receptors.[72] Further, increased dopaminergic response to food stimuli has been found to correlate with binge-eating behavior in obese subjects.[73] Thus, a reduced dopamine-stimulated D_2 receptor-mediated response to food may result in the need to eat more palatable food (to promote dopamine responses) and a greater desire and heightened dopamine activation in response to sight of food (possibly resulting from the inhibition of frontal cortex–dependent executive control).

Dietary-induced obese animals show low basal dopamine levels that increase in response to palatable food, but not to standard rodent food.[74] Other studies suggest that cholecystokinin-deficient Otsuka Long Evans Tokushima Fatty (OLETF) rats, which are obese, have

decreased D_2 receptor binding in the nucleus accumbens shell,[75] and that D_2 receptor activation contributes to the avidity for sucrose in obese OLETF rats.[76]

How Could Chronic, Excessive Sugar Intake Cause Abnormalities in Dopamine and D_2 Receptor Signaling?

Sucrose likely activates dopamine release in the brain via several mechanisms. One way involves activation of sweet receptors (T1R2 and T1R3) present in the tongue and gut.[77] Sweet taste from either sucrose or sucralose will elicit taste preference and a dopaminergic response in the nucleus accumbens.[78] The importance of taste receptors has also been suggested by the use of sham feeding in which a gastric fistula minimizes the absorption of food. Under these circumstances, sucrose can still increase extracellular dopamine in the nucleus accumbens.[31,41,79] However, the taste receptor is not the only mechanism for inducing dopamine release in sucrose-fed rats. Hence, mice lacking functional taste receptors (trpm5$^{-/-}$ knockout mice in which signaling via the sweet taste receptors is prevented) still show a dopamine response and preference for sucrose, whereas the dopamine response to sucralose is eliminated.[78] Likewise, mice genetically lacking the T1R3 in their taste buds and gut continue to show a preference for sucrose even if it is provided via gastric infusion.[80] The observation that artificial sugars, such as sucralose, can stimulate dopamine in the nucleus accumbens of normal mice may provide one explanation as to why earlier studies comparing sucrose with aspartame showed no difference in ADHD symptoms.

The observation that mice lacking sweet receptors continue to prefer sucrose and manifest an increased striatal dopamine response suggests that sucrose may have effects on mesolimbic dopamine signaling as a consequence of its metabolism. Sucrose is degraded by sucrase in the gut to fructose and glucose, which are then absorbed and metabolized. Thus, the effects of sucrose, as well as HFCS, likely relate to the metabolic effects of glucose and/ or fructose. Studies led largely by Ackroff et al[81,82] suggest that rats demonstrate taste preference for both glucose (and its polymers [Polycose]) and fructose, even if they are given these sugars postorally (which is performed by coupling the administration with an orally flavored substance). Intake of both glucose[83] and fructose[84] can be reduced by the injection of dopamine receptor antagonists in the nucleus accumbens. Studies assessing "sugar addiction" have been performed using glucose, and the findings suggest that if glucose is provided intermittently, it can induce an addiction-like syndrome, with bingeing behavior, withdrawal-like symptoms in response to naloxone, and a downregulation of D_2 receptors.[35,43] These data suggest that both glucose and fructose can elicit dopamine responses that might have relevance to understanding ADHD.

While fructose and glucose show some similarity in their effects, studies suggest that they may mediate their effects on taste preferences via different pathways.[85] In rats, for example, aqueous glucose is preferred over fructose due to stronger postoral mechanisms, whereas fructose may elicit a stronger oral response.[81,86] Fructose and glucose also differ markedly in their metabolism (Figure 3). Unlike glucose, fructose readily induces intracellular phosphate and adenosine tri-phosphate (ATP) depletion during its metabolism, as the initial phosphorylation of fructose to fructose-1-phosphate by fructokinase results in the rapid consumption of ATP.[87] In contrast, during glucose metabolism, ATP depletion never occurs, as there is a negative feedback system that prevents excessive phosphorylation. The decrease in intracellular phosphate that occurs during fructose metabolism also results in the stimulation of adenosine monophosphate (AMP) deaminase, which converts AMP to inosine monophosphate (IMP) and eventually to uric acid. Uric acid is rapidly generated in the liver with a rise in serum uric acid that peaks within 1 hour after fructose ingestion.[88] In addition,

some studies suggest that fructose may be metabolized in the hypothalamus; if so, it should also result in intracellular uric acid generation at this site.[89,90]

Acutely increasing uric acid in rats has been reported to increase extracellular dopamine in the substantia nigra.[91] Theoretically, this should inhibit dopamine neuronal firing due to stimulation of inhibitory somatodendritic D_2 autoreceptors on the dopamine neurons. However, acutely increasing uric acid also stimulates locomotor activity.[92] This observation suggests that dopamine in the terminal fields is also elevated and stimulates postsynaptic D_1 and D_2 receptors to cause locomotor activation. In turn, persistent receptor activation could result in downregulation of dopamine receptors in striatum. Uric acid may increase dopamine by blocking metabolism of dopamine to its oxidative end product, dihydroxyphenylacetic acid.[91,93]

Additional lines of evidence support a possible role for uric acid in ADHD. First, children with ADHD have higher serum uric acid levels than controls. Specifically, in a study of 40 girls and 50 boys (aged 3.5–4.5 years), serum uric acid levels correlated with hyperactivity, short attention span, impulsivity, and anger control.[94] Low-level lead intoxication has been linked with increased risk for ADHD,[95] and lead intoxication is another mechanism for increasing uric acid levels.[96,97] Attention-deficit/hyperactivity disorder is also much more common in boys than girls, which is consistent with the fact that boys have higher uric acid levels than girls.[94]

Fructose is thought by some to be the critical component in sucrose and HFCS that drives obesity and metabolic syndrome.[98–100] Fructose may induce obesity via several mechanisms, including by failing to stimulate leptin secretion compared with glucose[101] and by inducing insulin and leptin resistance, the latter resulting in impaired leptin signaling to the hypothalamus.[102] Because insulin and leptin inhibit dopamine signaling, the induction of resistance to these hormones might facilitate increased dopamine signaling.[23] Fructose can also induce ATP depletion in the liver,[103–105] and ATP depletion in the liver has been shown to stimulate hunger.[106–108] Fructose also lowers ATP in the hypothalamus, activates AMP kinase, and inhibits acetyl-CoA carboxylase (by phosphorylating it), which lowers malonyl-CoA, resulting in increased POMC (pro-opiomelanocortin) and hunger.[89,90] Furthermore, a recent study using fMRI reported that glucose increased cortical activation in reward-control areas, whereas fructose had opposing effects.[109] Thus, it remains possible that fructose and glucose may have distinct mechanisms by which they alter dopamine signaling.

While these latter studies implicate fructose as a key factor in how sucrose may be related to obesity and ADHD, the binge behavior and dopamine signaling that can be induced by intermittent exposure to glucose could also play a major contributory role. Clearly, more studies are needed to determine the role of these 2 sugars alone and in combination as they may be related to behaviors associated with ADHD.

Conclusion

We postulate that sugar acutely increases dopamine, which, over time, leads to a reduced number of D_2 receptors and possibly a reduction in extracellular dopamine itself, leading to desensitization of this dopamine signaling axis. These effects would not be due to the acute effects of sugar, but rather would occur over weeks to months with chronically elevated and intermittent sugar ingestion (Figure 2). If this is true, then children with ADHD may ingest more sugar than other children in an attempt to correct the dopamine-deficient state, resulting in excessive sugar intake that could result in "sugar addiction" and increase their risk for obesity. These children would manifest with slightly higher uric acid levels,

reflecting the increased sugar intake. Caregivers may consider that the acute effects of sugar are the cause of ADHD. However, the administration of sugar over days to weeks would be unlikely to induce greater symptoms of ADHD, especially if sucrose intake is compared with artificial sweeteners that can also elicit a dopamine response. Therefore, a potential causal relationship between sucrose and ADHD could have been missed in prior studies.

The observation that ADHD represents a dopamine-deficient state could explain why treatments that increase dopamine levels in the nucleus accumbens, such as amphetamine and methylphenidate, improve symptoms, at least acutely.[3] However, based on the increasing evidence for D_2 receptor desensitization/downregulation as a mechanism underlying ADHD, one might expect these drugs to have an enhanced potential to cause addiction. Indeed, this issue has been raised with modafinil, which increases extracellular dopamine and has been used to treat narcolepsy.[110] Dopamine receptor agonists have also been reported to lead to gambling and addictive behavior in subjects with Parkinson's disease.[111] Further studies evaluating the role of dopamine receptor agonists in ADHD are needed.

We recommend specific experimental and clinical studies to test our hypothesis (Table 1). If it is determined that ADHD is a consequence of the marked increase in intake of added sugars, then public health measures to reduce sugar intake are indicated, especially in young children (aged < 7 years), who are most predisposed to developing ADHD. As ADHD can be associated with impaired school performance, antisocial behavior, and drug addiction, the importance of such an approach could be far reaching.

Acknowledgments

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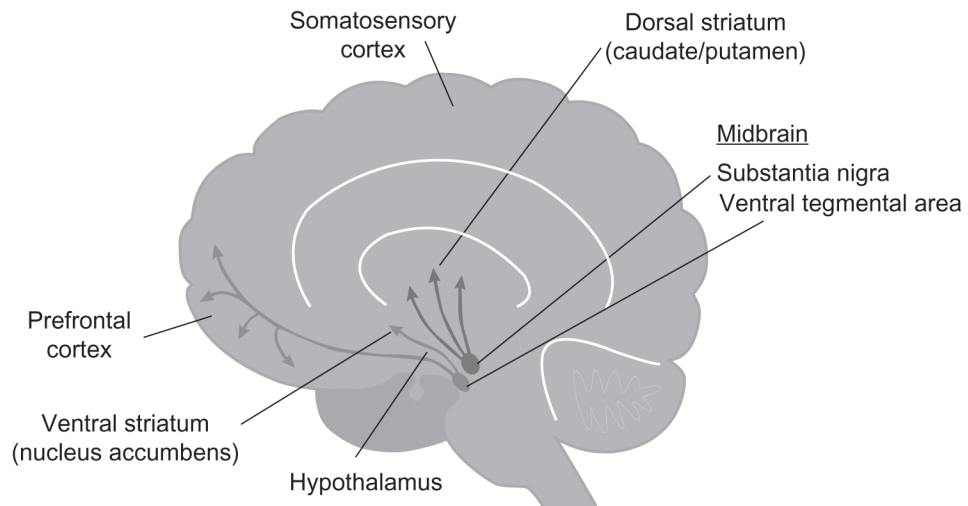
Figure 1.
Midsagittal view of the human brain with dopamine pathways. The light gray lines show the mesolimbic pathway (ventral tegmental area to the prefrontal cortex and nucleus accumbens). The dark gray lines show the nigrostriatal pathway (substantia nigra to the dorsal striatum or caudate/putamen).
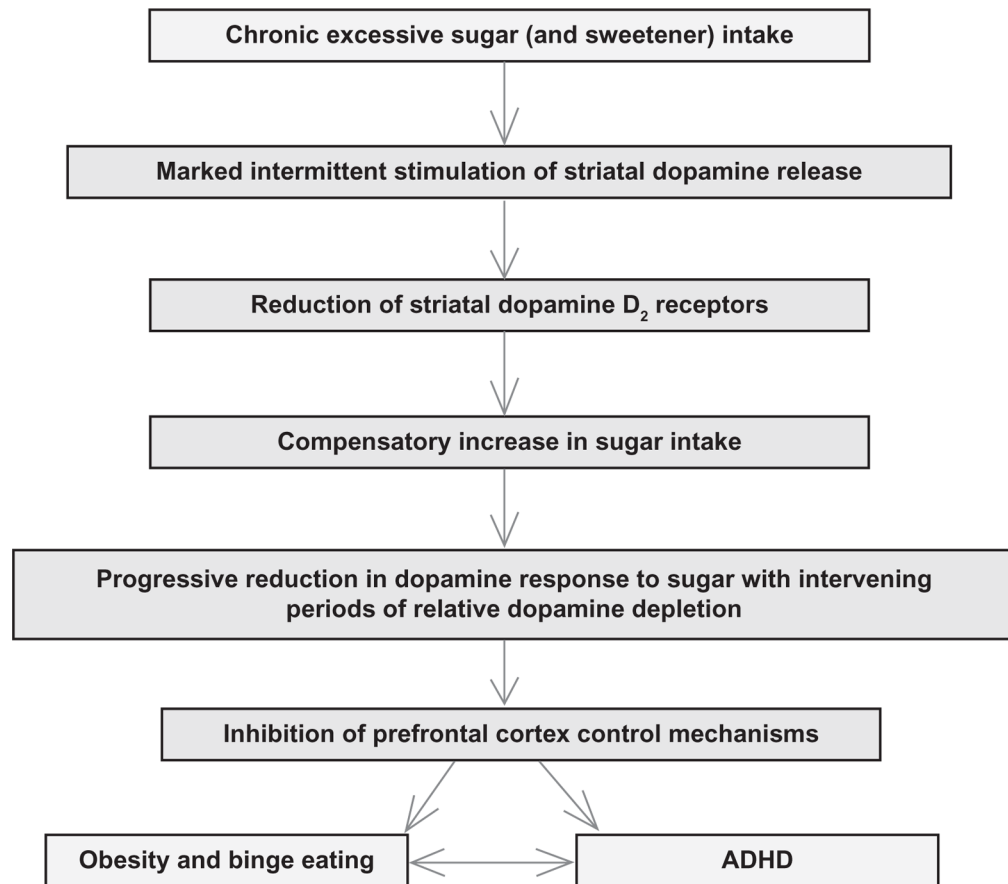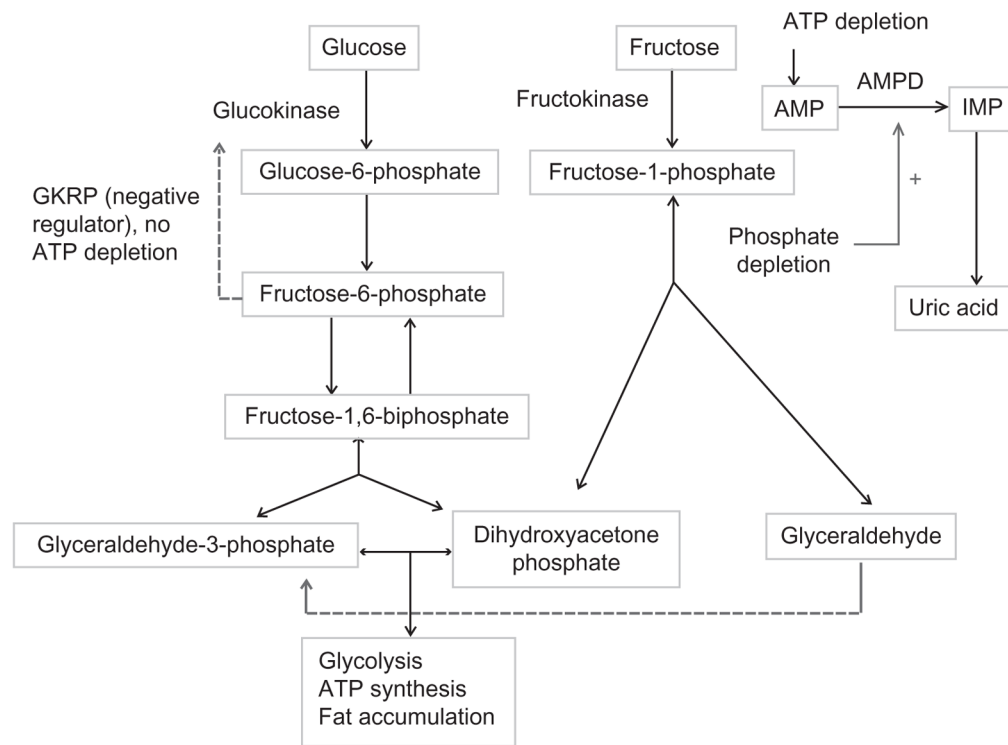
Figure 2.
Proposed pathway for the development of symptoms associated with ADHD. The ingestion of sugar or other sweeteners results in an acute elevated dopamine release in the striatum associated with reward. This may lead to increasing sugar ingestion, which, over weeks to months, results in a reduction in striatal D_2 receptors. To compensate, increased sugar intake occurs, resulting in dopamine responses that slowly decrease over time. In the periods between sugar ingestion, extracellular dopamine levels may progressively decrease, leading to a low dopamine state. The low dopamine state results in inhibition of frontal cortex control mechanisms, leading to ADHD symptomatology and obesity-prone binge-eating behavior.
Abbreviation: ADHD, atention-deficit/hyperactivity disorder.

Figure 3.
Differences between glucose and fructose metabolism. Glucose is phosphorylated by glucokinase into glucose-6-phosphate, which is isomerized to fructose-6-phosphate as part of the glycolysis for ATP production in the mitochondria and fat accumulation. Excessive fructose-6-phosphate generation activates GKRP for glucokinase inhibition. Unlike glucose, fructose metabolism is not negatively regulated. Therefore, fructose readily induces intracellular phosphate and ATP depletion during its metabolism by fructokinase. The decrease in intracellular phosphate that occurs during fructose metabolism also results in the stimulation of AMPD, which converts AMP to IMP and uric acid.
Abbreviations: AMP, adenosine monophosphate; AMPD, adenosine monophosphate deaminase; ATP, adenosine triphosphate; GKRP, glucokinase regulatory protein; IMP, inosine monophosphate.

Table 1

Proposed Studies to Evaluate the Potential Role of Chronic Sugar Intake in the Pathogenesis of ADHD

1	Reevaluate the relationship between chronic excessive intake of sugar in childhood and later development of ADHD and binge eating.
2	Determine if individuals with low sugar ingestion in childhood are relatively protected from developing ADHD.
3	Evaluate the effect of chronic excessive sugar intake on development of ADHD-like symptoms in experimental animals.
4	Conduct studies to determine the effect of fructose versus glucose in inducing a reduction in striatal D_2 receptors.
5	Conduct studies to separate the effect of artificial sweeteners from that of nondietary sugars in inducing a long-term reduction in D_2 receptors and inhibition of frontal lobe control mechanisms.

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.