

## Is Sugar a Gateway Drug?

Mitchell B Liester<sup>1</sup> and  
Jenna D Moore<sup>2</sup>

### Abstract

Addiction is a chronic, relapsing disorder with genetic, biochemical and psychosocial antecedents. Chronic use of drugs of abuse results in characteristic biochemical changes in the mesolimbic pathway of the brain including reduced extracellular dopamine levels and down regulation of dopamine 2 receptors. Similar biochemical changes have been identified with consumption of high concentrations of sugar. Cross-sensitization between sugar and drugs of abuse has been demonstrated to occur. This raises the possibility that sugar could act as a gateway drug, increasing the subsequent risk of becoming addicted to drugs of abuse. This article examines the research that indicates sugar can act as a gateway drug.

**Keywords:** Mesolimbic pathway; Dopamine; Homeostasis; Allostasis; Reward deficiency syndrome

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### Introduction

In 2012, more than 22 million people in the U.S. aged 12 or older suffered from substance abuse or dependence [1]. The development of addictions is associated with characteristic changes in the mesolimbic pathway (MLP) in the brain [2, 3]. Factors known to influence the MLP and increase the risk of addictions include genetic polymorphisms and environmental influences [4, 5]. Foods and beverages containing high concentrations of sugar are examples of the latter [6]. Excessive sugar consumption causes changes in the MLP that mimic the effects of drugs of abuse (DOA) [7, 8]. Furthermore, changes in the MLP resulting from the excessive ingestion of sugar have been demonstrated to increase the likelihood of future drug use [9, 10]. This raises the question, can sugar act as a gateway drug?

### Method

PubMed and reference lists were searched for articles published until October 1, 2015 using the keywords: sugar and addiction. Secondary searches included articles cited in sources identified by the previous search.

### Addiction and the mesolimbic pathway

*Drug addiction* has been described as a chronically relapsing disorder characterized by compulsion to take one or more drugs of abuse (DOA) with loss of control over drug intake and continued use despite negative consequences [11, 12]. Kalivas and Volkow [13] described three stages of addiction: (1) Acute drug effects,

(2) A transition from recreational use to repetitive use, and (3) End-stage addiction characterized by an overwhelming desire to use the drug, a diminished ability to control drug-seeking, and reduced pleasure from other, everyday rewards.

The biochemical etiology of addiction has been linked to neurochemical and neurophysiological changes in the mesolimbic pathway (MLP). More than half a century ago, electrical stimulation of the brain was demonstrated to produce positive reinforcement in rats [14]. Subsequently, the medial forebrain bundle (an older name for the mesolimbic pathway) was suggested as the final common pathway for reward messages involving a variety of forebrain reward sites [15]. The MLP, also known as the "mesolimbic dopamine system" [3], has been demonstrated to be involved in motivation, pleasure, and reward [16].

The MLP is formed by dopaminergic neurons originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) [17, 18]. Dopamine (DA) is known to be an important neurotransmitter associated with reward [19-22]. Pleasurable stimuli [23, 24] and natural rewards [25] trigger the release of DA in the NAc shell.

Drugs of abuse (DOA) such as alcohol, nicotine, psychostimulants, opiates, and marijuana, also stimulate DA release in the NAc [24-26]. In fact, all DOA have been demonstrated to trigger DA release in the NAc [3, 21, 27, 28].

- 1 Department of Psychiatry, Monument Canada
- 2 Department of Nutrition, University of Colorado at Colorado Springs, Canada

**Corresponding author:** Mitchell B Liester

✉ liester@aol.com

Department of Psychiatry, Monument, CO 80132, Canada.

**Tel:** 7194880024

**Fax:** 71904886672

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DOA increase extracellular DA in the NAc through a variety of mechanisms. For example, cocaine blocks the DA transporter (DAT) [29] whereas amphetamines induce DA release from pre-synaptic neurons [30]. Opiates inhibit Gamma-Aminobutyric acid (GABA) interneurons that in turn inhibit mesolimbic DA neurons, thus promoting DA release [2].

Release of DA in the NAc is associated with pleasure and reward [16]. The more rapidly DA levels rise, the stronger the reinforcing effect of the drug [31].

Chronic or repeated use of DOA produces neurochemical and neurophysiological alterations in the MLP associated with addictions. These changes include decreased levels of extracellular DA [32] and down regulation of DA 2 receptors (D2Rs) [33].

Reduced D2R density has been found in chronic users of DOA. Morphine and cocaine decrease NAc D2R mRNA in rats [34, 35]. D2Rs are down regulated in cocaine addicts [36], methamphetamine abusers [37], and alcoholics [33].

High numbers of D2Rs have been suggested to have a protective role in alcoholism [38]. In rats, artificially increasing the number of D2Rs reduces alcohol and cocaine intake [39-41]. These findings suggest the number of D2Rs correlates inversely with self-administration of DOA's [26].

To summarize these findings, chronic use of DOA results in reduced levels of extracellular DA and decreased D2R density in the MLP. Low levels of D2Rs are associated with increased consumption of DOA and addiction [37, 40, 41] whereas normal or high levels of D2Rs are associated with low craving behaviors and decreased consumption of DOA [38].

### Homeostasis and the brain reward cascade

More than two decades ago, Blum and Kozlowski [42] proposed the existence of a "Brain Reward Cascade" or BRC. The BRC is an interactive cascade of neurotransmitters that influences DA release in the MLP. The BRC begins with the release of serotonin (5-HT) in the hypothalamus. 5-HT then triggers the release of met-enkephalin in the VTA. Binding of met-enkephalin to opiate receptors inhibits the release of GABA. This reduction of the inhibitory neurotransmitter GABA disinhibits DA release, resulting in increased levels of extracellular DA in the NAc [23, 43].

Under normal conditions, release of neurotransmitters along the BRC creates a homeostasis within the MLP. However, under abnormal circumstances, such as during chronic self-administration of DOA, this homeostasis is disrupted. Evidence for this homeostasis model comes from a study by Koob [44] who found rats allowed to self-administer ethanol during acute withdrawal self-administered just enough ethanol to return extracellular DA levels in the NAc to predependence baseline levels.

### Reward deficiency syndrome

Genetics contribute significantly to vulnerability to addictions. Heritability for addiction has been estimated at 50% [45] with multiple genes contributing to this predisposition.

Numerous genetic polymorphisms have been linked with the development of addictions. These include genes for: the serotonergic 2A receptor (5HT2AR), serotonergic transporter (5HTTLPR), dopamine D1 receptor (D1R), dopamine D2 receptor (D2R), dopamine D3 receptor (D3R), dopamine D4 receptor (D4R), dopamine transporter (DAT), the catechol-O-methyltransferase (COMT), mono-amine oxidase (MOA), mu-opiate receptor (MOR), and GABA-B<sub>3</sub> genes [46]. These polymorphisms produce dopaminergic hypofunction in the MLP [46], which has been hypothesized to increase the use of DOA in order to raise DA levels [4].

Blum and colleagues [43] proposed that genetic polymorphism of the D2R is associated with hypodopaminergic functioning in the NAc. This produces a condition they labeled "Reward Deficiency Syndrome" (RDS) [47]. RDS is associated with polysubstance abuse [43, 46].

D2 agonists alter extracellular DA levels and D2R density in the MLP. Both the dose of the D2 agonist and the frequency of administration of the D2 agonist are important factors that influence extracellular DA levels and D2R density. Constant stimulation with low doses of D2 agonists results in proliferation of D2Rs [23]. However, chronic stimulation with more potent D2 agonists results in decreased D2R density [48]. Chronic use of DOA also results in reduced D2R density [33, 37]. Intermittent administration of DOA leads to a more pronounced increase in extracellular DA levels than occurs following acute administration of these drugs [25].

Reduced D2R density produces a hypodopaminergic state that is functionally similar to RDS. Reduced DA levels in addicts, along with increased sensitivity to the DA enhancing effects of DOA, have been proposed as mechanisms leading to drug-seeking behavior and subsequent addiction [26].

Dopaminergic hypofunction has been proposed as a common etiologic factor contributing to a number of impulsive, compulsive, and addictive disorders [47]. The proposed mechanism involves the utilization of substances and/or behaviors that stimulate the release of mesolimbic DA in order to compensate for the underlying dopaminergic hypofunction, thus restoring homeostasis to this system [23]. This seeking out of DA may underlie the craving and bingeing that occur with DA-stimulating substances [23].

### Allostasis

Koob and Le Moal [49] conceptualized addiction as a "cycle of spiralling dysregulation of brain reward systems that progressively increases, resulting in compulsive use and loss of control over drug-taking" (p. 97). These investigators proposed that a continuous process of hedonic homeostatic dysregulation alters DA's normal set point, resulting in stabilization at a new, pathological set point. This occurs through *allostasis*, which they defined as "the process of maintaining apparent reward function stability by changes in brain reward mechanisms" [49] (p. 97). In other words, repeated stimulation of DA by DOA results in a restabilization of MPL dopaminergic tone at a lower, pathological set point.

### Food's effects on the MLP

The same neurobiological pathway involved in addiction to DOA modulates food consumption and can result in addiction to food [50-53]. Food triggers DA release in the MLP [25]. This effect diminishes, however, when the food is no longer novel due to repeated access (unless the animal is food deprived) [54-56]. Thus, extracellular DA levels in the MLP adapt to repeated presentation of the same food reward, whereas novel foods continue to stimulate DA release [25].

Overconsumption of palatable food results in downregulation of D2Rs and a state of reward hyposensitivity that mimics the effects of chronic administration of DOA. This reduction in D2Rs is similar in magnitude to the reduction reported in drug-addicted subjects [57].

### Sugar's effects on extracellular DA levels in the MLP

Sugar produces biochemical changes in the MLP similar to those produced by DOA. For example, Hajnal et al. [58] found that rats fed oral sucrose solutions at concentrations of 0.03 M, 0.1 M, and 0.3 M experienced a concentration-dependent increase in extracellular DA levels in the NAc that was statistically significant ( $P < 0.01$ ). Also, Rada et al. [56] showed that sucrose-dependent rats released more DA in the NAc following sucrose ingestion than control rats that were not sucrose-dependent. The difference in DA release was statistically significant ( $P < 0.03$ ).

Acute administration of D2 antagonists causes a dose-dependent inhibition of sucrose intake in rats [59-61].

Habituation to the stimulatory DA response in the NAc shell occurs after a single pre-exposure to the same taste or food in rats [54]. However, rats fed sucrose intermittently continue to produce increased levels of DA [56, 62]. Also, the amount of DA released in the NAc is proportional to the sucrose concentration, rather than the volume of sucrose ingested [58]. Foods with higher concentrations of sucrose trigger greater amounts of DA release than foods with lower concentrations of sugar, and intermittent exposure to sucrose produces higher levels of DA than continuous exposure.

### Sugar's effects on DA receptors

Intermittent ingestion of sugar has been demonstrated to reduce D2Rs in rats. Colantuoni and colleagues [7] found that rats fed a 25% glucose solution with chow for 12 hours each day doubled their glucose intake in 10 days. After 30 days, receptor binding was evaluated and compared with chow-fed controls. D2R binding decreased significantly in the glucose-fed rats. Bello et al. [63] found that food-restricted rats fed a diet supplemented with sucrose (0.3 M) for 2 hours a day exhibited decreased D2R binding in the NAc shell after 7 days. Spangler et al. [64] reported rats placed on a chronic schedule of intermittent binging on a 10% sucrose solution exhibited decreased levels of D2R mRNA in the NAc compared with ad libitum chow controls.

### Cross-sensitization between sugar and drugs of abuse

Drug-induced sensitization may lead to increased self-administration of the same drug. Sensitization has been suggested to play a role in drug addiction [65]. Additionally, sensitization to one drug can lead to increased self-administration of another drug, a process known as "cross-sensitization" [6].

Cross-sensitization has been demonstrated between various DOA. Amphetamines cross-sensitize to cocaine or phencyclidine [66]. Cocaine cross-sensitizes to alcohol [67] Heroin cross-sensitizes to the synthetic cannabinoid receptor agonist WIN55212.2 [68].

Several studies have found intermittent sugar intake cross-sensitizes to drugs of abuse. Rats fed a 10% sucrose solution cross-sensitize to amphetamine [8] and rats given access to granulated sucrose cross-sensitize to cocaine [69]. Rats provided intermittent access to 10% sucrose, then forced to abstain, show increased intake of alcohol [9]. Also, rats that prefer sweet-taste will self-administer cocaine at a higher rate [70]. These studies indicate that sugar cross-sensitizes to DOA.

Avena & colleagues [6] have suggested that cross-sensitization between sugar and DOA may contribute to addiction by enhancing responsiveness to DA in the MLP. When one drug leads to the increased use of another drug, this is referred to as "consummatory cross-sensitization" or "gateway effect" [6].

### The gateway hypothesis

The idea that developmental stages and sequences of drug use exist was first proposed nearly four decades ago [71-73]. This idea suggests that a progressive and hierarchical sequence of stages of drug use can be described [74-76]. The basic premise of the developmental stage hypothesis is that involvement in various classes of drugs follows definite pathways and individuals who ingest one drug are at risk of progressing to the use of another drug [74].

The term *gateway drug* appeared in the 1980's. This term was initially used to refer to alcohol and cigarettes, two licit drugs that were used prior to the use of illicit drugs. Later, the term *gateway drug* was applied to illicit drugs, such as marijuana, as well [74].

The *Gateway Hypothesis* suggests the use of some drugs (i.e., gateway drugs) increases the subsequent risk of using other drugs [74, 77]. There are three propositions to the Gateway Hypothesis: (1) a developmental sequence of involvement with different classes or categories of drugs exists, (2) the use of a drug earlier in the sequence is associated with an increased risk or likelihood of use of a drug later in the sequence, and (3) the use of a drug earlier in the sequence causes the use of a drug later in the sequence [74]. Examples include the use of tobacco or alcohol leading to marijuana use [74] or nicotine leading to cocaine use [78].

The mechanism by which the use of one drug leads to the increased use of another drug remains controversial. Degenhardt et al. [79] suggested etiological factors might include drug avail-

ability and attitudes of drug users. Schenk [77], on the other hand, suggested sensitization provides a mechanism for the progression of drug use both within and across drug classes. Numerous studies have demonstrated that exposure to certain drugs produces a sensitized behavioral response to those same drugs, and also produces neuroadaptive changes in DA neurotransmission [77]. Nicotine and alcohol, for example, have been demonstrated to produce a sensitized response to DA [77].

Cross-sensitization may contribute to the process of a gateway drug increasing the risk of subsequent use of other drugs [77]. Cross-sensitization occurs when administration of one substance results in sensitization to another drug [6]. This cross-sensitization involves one drug priming the MLP, so that subsequent use of a different drug produces greater than expected release of DA. One example would be pretreatment with nicotine sensitizing mice to alcohol, resulting in a greater release of DA than would otherwise be expected [80].

### Is sugar a gateway drug?

Erickson [18] defined a drug as “any chemical other than food or water that produces a therapeutic or nontherapeutic pharmacological action in the body” (p. 93). Based upon this definition, sugar would not be classified as a drug, because it is generally considered to be a food, and foods are excluded from the category of drugs.

However, as Tupper [81] has emphasized, definitions of “drugs” and “foods” are strongly influenced by political and cultural factors. Whether we define sugar as a drug or a food is strongly influenced by factors other than the existing scientific evidence regarding its pharmacological effects.

More important than semantics, however, is the understanding of the research previously cited in this article that indicate sugar's effects on the MLP mimic the effects of numerous drugs of abuse including cocaine, heroin, nicotine, and alcohol. If we are willing to consider the possibility that sugar acts like a drug on the MLP, we can then begin to examine whether sugar acts as a gateway drug.

As previously discussed, the Gateway Hypothesis consists of 3 propositions. Do these propositions apply to sugar? We can look at each of these three propositions individually in relationship to sugar.

### Proposition 1 - “There is a developmental sequence of involvement with different classes or categories of drugs.”

Much of the research on the addictive nature of sugar has been performed on rats in a laboratory setting. This makes it challenging to determine whether a developmental sequence exist involving different classes or categories of drugs. Rats in a laboratory setting do not generally have access to a wide range of different classes of drugs. However, evidence suggests that the ingestion of sugar does increase the subsequent use of drugs of abuse.

Avena et al. [9] found that rats given intermittent access to 10% sucrose subsequently consumed more ethanol than rats given ad libitum access to sucrose ( $P < 0.05$ ). Rats provided intermittent ac-

cess to sugar also show signs of cross sensitization with amphetamine [8] and cocaine [69].

These studies suggest the use of sugar can lead to the increased use of drugs of abuse.

### Proposition 2 - “The use of a drug earlier in the sequence is associated with an increased risk or likelihood of use of a drug later in the sequence.”

Studies have demonstrated that a rat's level of sucrose preference can predict its desire to self-administer cocaine [82]. Furthermore, studies have demonstrated cross-sensitization between sugar and drugs of abuse [8, 9, 70, 83].

Several studies have reported a positive correlation between the intake of sugar or saccharin solutions and the self-administration of morphine, cocaine, and amphetamine [69, 83-85]. Also, the acquisition of amphetamine self-administration has been shown to be more rapid in high sucrose feeder rats than in low sucrose feeders [84]. Sugar has also been demonstrated to produce a gateway effect for alcohol [9] and cocaine [70].

These findings support the proposition that sugar intake is associated with an increased likelihood of using drugs of abuse.

### Proposition 3 - “The use of a drug earlier in the sequence causes the use of a drug later in the sequence.”

Evidence supporting this proposition comes from previously cited research demonstrating that increased release of DA in the NAc following the ingestion of high concentrations of sugar leads to down-regulation of D2Rs [7, 63, 64]. This produces a hypodopaminergic state of allostasis [49]. The behavioral consequence of this state is an increased use of substances that trigger DA release in an effort to regain homeostasis in the MLP [23]. Ingestion of DOA releases DA in the NAc [3, 21, 24-28]. Thus, the ingestion of food and drinks containing high concentrations of sugar would be expected to contribute to the repeated use of DOA in an attempt to restabilize MLP DA levels at a homeostatic level.

## Discussion

Although sugar is not ordinarily viewed as a drug of abuse, intermittent binging with sugar triggers neurochemical responses in the MLP that parallel those produced by DOA. Furthermore, evidence has demonstrated sugar may be addictive when consumed in a binge-like manner [6].

Although quantitatively different, the neurochemical changes produced by the intermittent ingestion of sugar are qualitatively similar to the changes produced by DOA in the MLP [6]. These include increased release of DA [54, 56, 58], reduced D2R mRNA [64], and down-regulation of D2Rs [7, 63]. The resultant hypodopaminergic state is associated with increased drug seeking [49].

Cross-tolerance has been demonstrated between sugar and DOA [8, 9, 70, 83]. These findings suggest the repeated ingestion of

sugar, particularly in high concentrations, may lead to “gateway effects,” resulting in increased use of DOA. Withdrawal effects of sugar parallel those observed with drugs of abuse [6, 86]. Thus, tolerance and withdrawal, the two hallmarks of dependence, have been demonstrated to occur following the repeated ingestion of sugar.

Despite the evidence supporting sugar’s role as a gateway drug, several limitations to this review must be noted. First, some researchers have challenged the validity of the Gateway Hypothesis. In a prospective study, Tarter et al. [87] found that 22.4% of subjects who used marijuana did not exhibit the gateway sequence. In these individuals, marijuana use was not preceded by the use of licit substances, leading the authors to conclude the gateway sequence is not an invariant pattern among drug-using youth.

Morral et al. [88] proposed an alternate “common factor model” of drug use. This model suggested that progression from marijuana to other drugs could be explained by the order in which individuals have the opportunity to use these drugs, without assuming that marijuana contributes to the risk of using “hard drugs.”

Degenhardt et al. [79] analyzed drug use patterns using World Health Organization (WHO) and World Mental Health (WMH) Surveys. In this study of 85,088 individuals from 17 countries, the authors found factors other than the Gateway Effect contributed to the ordering and progression of drug use. These factors included: exposure or access to certain drugs, attitudes toward certain drugs, background prevalence of drug use, age of onset, and degree of exposure to certain drugs.

Another limitation of this study is the use of the term “drug” when referring to sugar. This application of the term “drug” is likely to provoke controversy, as sugar has historically been viewed as a food, rather than a drug. However, numerous studies have demonstrated that sugar produces effects on the MLP similar to those produced by drugs of abuse. Thus, a reexamination of sugar’s potential role as a drug appears warranted, based upon the evidence provided in the afore-referenced articles.

Quantitative studies are needed to determine whether a threshold dose exists which transforms sugar from a pleasure-inducing food to a MLP-priming drug. Such studies should evaluate whether a dose or concentration of sugar can be identified that produces sufficient DA release in the MLP to cause allostasis, with the subsequent triggering of drug craving and drug seeking behaviors.

Also, a lack of specificity regarding the use of the term “gateway drug” is problematic. Some studies limit the definition of a gateway drug to licit substances only (e.g., alcohol and tobacco) whereas others include illicit substances (e.g., cannabis). In this article, the term “gateway drug” is used to refer to sugar, a substance that many would not consider to be a drug at all. Therefore, identifying sugar as a gateway drug is likely to be controversial.

Another limitation of this review is that the majority of research cited involves studies using rats as subjects. Although rats may respond to sugar as a gateway drug, additional studies are needed to determine if sugar exhibits similar effects in humans.

Variability in the types and concentrations of sugar utilized in referenced studies is a further limitation of this article. Additional studies are needed to clarify whether different sugars (e.g., monosaccharides, disaccharides, and polysaccharides) have similar or different effects on the MLP.

Most existing studies investigate only sugar’s short-term effects on the MLP and the subsequent use of DOA. Long-term studies are needed to investigate whether sugar’s effects on the MLP and on the subsequent use of DOA persist over longer periods of time (e.g., years).

Finally, the implication of the findings in this paper would indicate that any substance that triggers DA release in the MLP has the potential to be a gateway drug. Further research is needed to clarify whether all substances that trigger DA release in the MLP act as gateway drugs, or if only specific substances function as gateway drugs. The degree to which substances trigger DA release and the rate at which DA levels rise influence the reinforcing effects of these substances. Therefore, studies designed to evaluate sugar’s quantitative effects on DA levels in the MLP are likely to yield useful data.

## Conclusion

If sugar acts as a gateway drug, what implications does this have for future generations? Per capita soft-drink consumption has increased nearly 500% in the past 50 years [89] and consumption of high-fructose corn syrup increased >1000% from 1970 to 1990 [90]. The full impact of this increase in sugar intake on the BRC, the MLP, and addictive behaviors remains to be determined. Further research is needed to clarify sugar’s role as a gateway drug. Additionally, further research examining strategies for minimizing sugar’s adverse impact on the MLP and the subsequent development of addictions is recommended.

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