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Evidence for Modulation of Substance Use Disorders by the Gut Microbiome: Hidden in Plain Sight

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***Abstract*——The gut microbiome modulates neurochemical function and behavior and has been implicated in numerous central nervous system (CNS) diseases, including developmental, neurodegenerative, and psychiatric disorders. Substance use disorders (SUDs) remain a serious threat to the public well-being, yet gut microbiome involvement in drug abuse has received very little attention. Studies of the mechanisms underlying SUDs have naturally focused on CNS reward circuits. However, a significant body of research has accumulated over the past decade that has unwittingly provided strong support for gut microbiome participation in drug reward. β-Lactam antibiotics have been employed to increase glutamate transporter expression to reverse relapse-induced release of glutamate. Sodium butyrate has been used as a histone deacetylase inhibitor to prevent drug-induced epigenetic alterations. High-fat diets have**

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been used to alter drug reward because of the extensive overlap of the circuitry mediating them. This review article casts these approaches in a different light and makes a compelling case for gut microbiome modulation of SUDs. Few factors alter the structure and composition of the gut microbiome more than antibiotics and a high-fat diet, and butyrate is an endogenous product of bacterial fermentation. Drugs such as cocaine, alcohol, opiates, and psychostimulants also modify the gut microbiome. Therefore, their effects must be viewed on a complex background of cotreatment-induced dysbiosis. Consideration of the gut microbiome in SUDs should have the beneficial effects of expanding the understanding of SUDs and aiding in the design of new therapies based on opposing the effects of abused drugs on the host's commensal bacterial community.

***Significance Statement*——Proposed mechanisms underlying substance use disorders fail to acknowledge the impact of drugs of abuse on the gut microbiome. *β*-Lactam antibiotics, sodium butyrate, and high-fat diets are used to modify drug seeking and reward, overlooking the notable capacity of these treatments to alter the gut microbiome. This review aims to stimulate research on substance abuse–gut microbiome interactions by illustrating how drugs of abuse share with antibiotics, sodium butyrate, and fat-laden diets the ability to modify the host microbial community.**

I. Introduction

According to the National Survey on Drug Use and Health, approximately 20 million American adults had a substance use disorder (SUD) in 2017. The National Institute on Drug Abuse has estimated that abuse of tobacco, alcohol, and illicit drugs costs the nation ~$740 billion annually in expenses related to crime, lost work productivity, and health care (see following link on National Institute on Drug Abuse webpage: https://www.drugabuse.gov/drug-topics/trends-statistics/costs-substance-abuse). Therefore, SUDs constitute a serious threat to the public well-being. A great deal of research has been focused on achieving a better understanding of the mechanisms by which abused drugs exert their addictive properties to develop more effective treatments. Unfortunately, Food and Drug Administration–approved therapies for SUD at present remain limited to methadone, buprenorphine, and extended-release naloxone for treatment of opiate use disorder. The vast majority of research on the mechanisms underlying SUDs has focused on reward pathways in the brain and, more specifically, the circuits in the ventral tegmentum area (VTA) and nucleus accumbens (NAc) that are activated by drugs of abuse and use the neurotransmitters dopamine (DA) and glutamate for synaptic signaling. A better understanding of the central nervous system (CNS) sites that are hijacked by alcohol, tobacco, and illicit drugs would possibly lead to new treatment strategies for SUDs.

By focusing almost entirely on CNS mechanisms underlying SUDs, other possible mediators outside of the CNS may escape notice, thus remaining understudied and underappreciated. Emerging results provide evidence of peripheral mechanisms that can mediate complex reward-seeking behaviors previously assigned to the CNS. The pioneering research of Hoebel and colleagues provided some of the earliest evidence that bingeing on sugar solutions has effects that are similar to substance abuse in that it shows dependence- and withdrawal-like behaviors, it cross-sensitizes with amphetamine, and it releases DA in the NAc [reviewed in Avena et al. (2008, 2009, 2011)]. Additionally, de Araujo and colleagues have shown that gut stimulation with caloric nutrients induces robust striatal DA release (Ren et al., 2010; de Araujo et al., 2012; Ferreira et al., 2012). Mice fed high-fat diets do not show the calorie-dependent DA effluxes seen in mice fed low-fat diets and this high-fat–induced DA deficiency is restored by the dietary satiety messenger oleoylethanolamine (Tellez et al., 2013). More recently, these same investigators have identified the neural circuit for gut-induced reward by showing that optical activation of the right nodose ganglion causes release of DA in the striatum, sustains self-stimulation behavior, and conditions a place preference [conditioned place preference (CPP)] that maps to populations of well known reward neurons in the nigro-striatal pathway (Han et al., 2018). In a related study, Fernandes et al. (2020) demonstrated that the intragastric administration of sucrose sustains self-administration and increases the activity of VTA-DA neurons via the hepatic branch of the vagus nerve. These investigators also showed that optogenetic stimulation of the left nodose ganglion significantly increased the activity of VTA-DA neurons (Fernandes et al., 2020). These findings suggest that nutrients can exert effects that are reminiscent of the actions of drugs of abuse, such as ethanol and nicotine, which have been shown to directly increase the firing of VTA neurons (Juarez and Han, 2016), and also maintain self-administration and support development of a CPP. The notion that compulsive intake of drugs and food share neurobiological

ABBREVIATIONS: CLV, clavulanic acid; CNS, central nervous system; CPP, conditioned place preference; CTX, ceftriaxone; DA, dopamine; DA D_1R, DA D_1 receptor; DA D_2R, DA D_2 receptor; DAT, DA transporter; DOX, doxycycline; GHSR1a, growth hormone secretagogue receptor type 1a; GI, gastrointestinal; GLT1, glutamate transporter 1; HDAC, histone deacetylase; HFD, high-fat diet; mGluR2, metabotropic glutamate receptor 2; MINO, minocycline; NaB, sodium butyrate; NAc, nucleus accumbens; NIDA, National Institute on Drug Abuse; OM, Osborne-Mendel; Per1, period circadian regulator 1; SCFA, short-chain fatty acid; SUD, substance use disorder; TIG, tigecycline; VTA, ventral tegmentum area.

substrates, which involve impairments in DA pathways regulating reward sensitivity and incentive motivation, has long been debated, and supportive data have been reviewed (Volkow and Wise, 2005; Gregorowski et al., 2013; Volkow et al., 2013; Clasen et al., 2020a). More recently, it has emerged that non-nutritive drugs of abuse (e.g., cocaine, amphetamine) can directly influence neuronal activity in homeostatic feeding circuits (i.e., Agouti-related protein neurons of the arcuate nucleus of the hypothalamus) and increase mesoaccumbal DA signaling (Alhadeff et al., 2019). Betley and colleagues propose the coordination of hypothalamic Agouti-related neuropeptide neurons and midbrain DA circuits to form reciprocal networks in the modulation of the neural processing of rewards (Alhadeff et al., 2019) and affirm the close interplay between the compulsive intake of food and drugs of abuse.

Wise and Kiyatkin (2011) have provided evidence for peripheral input to the addictive properties of cocaine that do not involve feeding-reward circuits. These investigators hypothesized that the peripheral actions of cocaine can serve as conditioned interoceptive stimuli for the central actions of this psychostimulant (Wise and Kiyatkin, 2011). Using cocaine methiodide, a quaternary cocaine analog that does not cross the blood-brain barrier, they demonstrated that central DA and glutamate release can be elicited by the methiodide analog in rats previously trained to self-administer cocaine HCl but not in naïve rats (Wise et al., 2008; Wang et al., 2013; Wakabayashi and Kiyatkin, 2014). Cocaine methiodide forms a CPP in cocaine HCl experienced rats and reinstates lever pressing after extinction of cocaine HCl self-administration (Wang et al., 2013).

Taken together, the foregoing discussion establishes rationale for the operation of peripheral input into the central actions of addictive drugs. The close interplay between neural circuits for the rewarding properties of nutrients (i.e., fat and sugar) and drugs of abuse raises the possibility that the gut microbiome and the gut-brain axis may also be involved in SUDs. The purpose of this commentary therefore is to discuss a wealth of published information that implicates the gut microbiome in SUDs but without invoking a role for it. The schematic in Fig. 1 illustrates the main discussion points of this review. Although discussion of the gut-brain axis per se is beyond the scope of this overview, the interested reader is referred to numerous, excellent review articles on this subject (Cryan and O'Mahony, 2011; Mayer, 2011; Carabotti et al., 2015; Mayer et al., 2015; Dinan and Cryan, 2017; Cryan et al., 2019).

II. The Gut Microbiome and Drugs of Abuse

The bulk of the microbiome resides in the gastrointestinal (GI) tract and is composed of bacteria, microbes, viruses, and archaea. It has been estimated that the human GI system contains >1000 bacterial species and $\sim 4 \times 10^{13}$ microorganisms [same as number of human cells (Sender et al., 2016)], and gut microbiome expresses ~100 times as many genes as the host human genome (Savage, 1977; Hamady and Knight, 2009). Normal functioning of the gut microbiome is essential to the maintenance of human health. A disruption in the gut microbiome composition (i.e., dysbiosis) has been linked to numerous diseases, including cancer, diabetes, obesity, immune dysfunction, and inflammatory bowel disease (Pflughoeft and Versalovic, 2012; Shreiner et al., 2015). It is also emerging that gut microbiome dysbiosis can play a role in numerous neurologic [e.g., Parkinson disease, Alzheimer disease (Tremlett et al., 2017)] and psychiatric diseases [e.g., autism (Dinan and Cryan, 2017), depression, and anxiety (Foster and McVey Neufeld, 2013)] and in eating disorders (Seitz et al., 2019).

Research on gut microbiome involvement in SUDs lags well behind most other health disorders, but an increasing number of publications are documenting drug-induced alterations in it. Many drugs of abuse are well known to alter GI function through gut microbiome modifications, and examples of this include opiate-induced constipation (Nee et al., 2018) and cocaine-induced bowel ischemia (Riezzo et al., 2012). It is therefore relevant to opiate use that constipation causes gut dysbiosis, and treatments that relieve constipation (e.g., probiotics) restore changes in the gut microbiome caused by this bowel condition (Dimidi et al., 2017; Meng et al., 2020). With regard to cocaine, modulation of the gut microbiome can prevent intestinal ischemia/reperfusion injury (Yoshiya et al., 2011; Bertacco et al., 2017). Alcohol (Caton et al., 2015), cocaine (Billing and Ersche, 2015), and amphetamine (Lemieux et al., 2015) can significantly alter the appetite as well. In view of the profound effects that diet has on the gut microbiome (Singh et al., 2017; Hills et al., 2019; Ezra-Nevo et al., 2020; Wilson et al., 2020), it should come as no surprise that many drugs of abuse can disrupt the composition of the gut microbiome.

The greatest amount of progress in SUD-gut microbiome interactions has been made for alcohol. It is now known that the gut microbiome is significantly altered in humans after moderate consumption (Kosnicki et al., 2019; Stadlbauer et al., 2019) as well as in those with alcohol dependence (Mutlu et al., 2012; Leclercq et al., 2014; Dubinkina et al., 2017; Bjørkhaug et al., 2019). Chronic alcohol consumption changes the composition of the gut microbiome of nonhuman primates (Barr et al., 2018; Zhang et al., 2019b) and alters microbiome status in rodent models of alcohol seeking (Peterson et al., 2017; Jadhav et al., 2018), chronic consumption (Yan et al., 2011; Bull-Otterson et al., 2013; Labrecque et al., 2015; Fan et al., 2018; Wang et al., 2018b; Kosnicki et al., 2019; Xu et al., 2019; Bluemel et al., 2020),

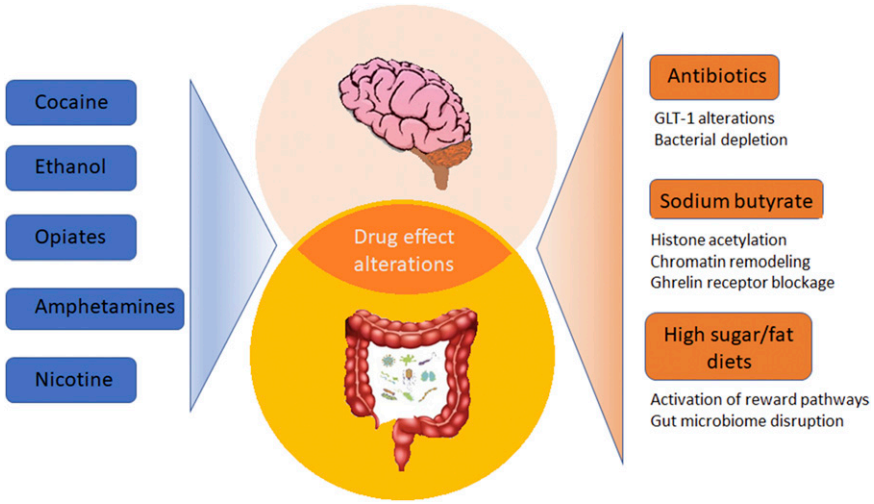

Fig. 1. Potential interactions between the brain and the gut microbiome in the modulation of the rewarding effects of drugs of abuse. Cocaine, ethanol, opiates, and psychostimulants have been shown to modify the gut microbiome. Beyond their suspected actions on the brain, β-lactam antibiotics, sodium butyrate, and hyperpalatable diets are also potent modifiers of the composition of the microbial communities in the gut. Studies on the mechanisms underlying substance use disorders have focused on CNS mechanisms, but the possibility exists for modulation of drug reward by the gut microbiome. This review offers alternative interpretations of research that has used antibiotics, sodium butyrate, and high-fat diets to modify drug reward and relapse by highlighting the profound effects of these agents on the gut microbiome. It is now clear that drugs of abuse cause significant alterations in the gut microbiome. Antibiotics, sodium butyrate, and high-fat diets also modify the gut microbiome. Therefore, when antibiotics, for example, are tested for effects on cocaine reward and relapse, consideration should be given to the possibility that the outcomes reflect the combined influence of both treatments on the gut microbiome.

and withdrawal (Xiao et al., 2018). Alcohol-induced dysbiosis has even been the subject of numerous review articles (Engen et al., 2015; Hillemacher et al., 2018; Leclercq et al., 2019; Qamar et al., 2019; Temko et al., 2017). With regard to opiates, chronic use is associated with substantial alterations in the gut microbiome of humans (Acharya et al., 2017; Xu et al., 2017) and nonhuman primates (Sindberg et al., 2019). Similarly, animal models of opiate dependence (Banerjee et al., 2016; Lee et al., 2018; Wang et al., 2018a, 2020) and analgesic tolerance (Kang et al., 2017; Zhang et al., 2019a) document drug-induced alterations in the gut microbiome. The effects of opiates on the microbiome have been the subject of several review articles as well (Akbarali et al., 2014; Akbarali and Dewey, 2017; Wang and Roy, 2017; Le Bastard et al., 2018; Wiss, 2019; Ren and Lotfipour, 2020). Emerging results have shown that cocaine causes dysbiosis in the gut microbiome of humans (Volpe et al., 2014) and rodents (Chivero et al., 2019; Scorza et al., 2019). Depletion of gut bacteria by treatment with a prolonged course of antibiotics increased sensitivity to cocaine CPP and enhanced its locomotor-stimulating properties (Kiraly et al., 2016). Nicotine (Allais et al., 2016; Chi et al., 2017; Wang et al., 2019; Nolan-Kenney et al., 2020), methamphetamine (Angoa-Pérez et al., 2020; Ning et al., 2017; Xu et al., 2017), bath-salts drugs (Angoa-Pérez et al., 2020), and cannabinoids (Al-Ghezi et al., 2019; Cluny et al., 2015) also cause significant dysbiosis in the gut microbiome. The effects of selected drugs of abuse on the gut microbiome have been reviewed recently (Meckel and Kiraly, 2019).

The first crucial step in assessing how drugs of abuse interact with the gut microbiome (e.g., documentation of drug-induced alterations in its composition and structure) has been partially achieved via the studies cited in the previous paragraph, but much work and many opportunities remain in this area. The next step involves determination of whether the gut microbiome modulates or plays active roles in SUDs. This second step has begun via studies that have used ceftriaxone (CTX), sodium butyrate (NaB), and high-fat diets (HFDs) to alter responses to a drug of abuse. However, these treatments were used for reasons completely unrelated to their ability to interact with the gut microbiome. These factors and the rationale for their use will be discussed below for cocaine, alcohol, opiates, and other drugs of abuse (e.g., methamphetamine, amphetamine, nicotine).

III. CTX and Other Antibiotics

CTX is a third-generation broad-spectrum β-lactam antibiotic. Its recruitment into studies of drugs of abuse was stimulated by a 2005 publication showing that CTX and other β-lactam antibiotics caused increases in the CNS expression of the glutamate transporter 1 [GLT1; (Rothstein et al., 2005)]. Rothstein and colleagues (2005) documented the ability of β-lactam drugs to increase transcription of the *GLT1* gene in both in vitro and in vivo experiments and demonstrated that CTX was neuroprotective in the G93A-SOD1 mouse model of amyotrophic lateral sclerosis. CTX was deemed neuroprotective by virtue of its ability to increase the reuptake of the excitatory neurotransmitter glutamate

via GLT1 and thereby reduce glutamate excitotoxicity (Rothstein et al., 2005). Beginning a few years after this publication and continuing to the present, a large number of studies have used CTX to modulate the rewarding effects of drugs of abuse, using it to increase expression of GLT1. It had already been demonstrated in a series of elegant studies that relapse to drug self-administration after extinction is mediated by downregulation of the GLT1 with a resulting increased secretion of glutamate in the NAc. The glutamate theory of addiction has been thoroughly discussed in numerous reviews (Koob and Nestler, 1997; Kalivas, 2004, 2009; Kalivas et al., 2009; Knackstedt and Kalivas, 2009; Torregrossa and Kalivas, 2008; Shen et al., 2014; Koob and Volkow, 2016; Spencer et al., 2016; Scofield, 2018). When using CTX strictly for its ability to increase expression of GLT1, the primary pharmacological action of this drug is overlooked. CTX is, after all, a powerful antibiotic that inhibits a large number of bacterial pathways. Two population-based metagenomics analyses revealed that use of antibiotics was significantly associated with alterations in microbiome composition, and the only drugs significantly associated with the differential abundance of specific bacterial genera were β-lactam antibiotics (Falony et al., 2016; Zhernakova et al., 2016). A recent review (Ferrer et al., 2017) illustrates the extremely broad effects of CTX and other β-lactams on the gut microbiome. CTX in particular alters nine different bacterial genera throughout the phyla of Actinobacteria, Bacteroidetes, Firmicutes, and Verrucomicrobia (Ferrer et al., 2017). Other antibiotics used to modify the addictive properties of drugs of abuse include primarily the β-lactams clavulanic acid (CLV), cefazolin, cefoperazone, ampicillin, and amoxicillin. The combination of CLV with amoxicillin (i.e., Augmentin) has also been used. CLV requires additional emphasis because it is stated to have minimal antimicrobial activity (and for this reason it is often combined with amoxicillin clinically), yet it retains the β-lactam moiety necessary to increase GLT1 expression (Rothstein et al., 2005). Therefore, when used by itself to alter the actions of a drug of abuse, CLV effects are generally attributed solely to alterations in GLT1. Despite this interpretation, CLV does have antimicrobial activity (Finlay et al., 2003; Ferrer et al., 2017) and has been linked to alterations in numerous bacterial genera within the phyla of Actinobacteria, Firmicutes, and Proteobacteria (Ferrer et al., 2017). The tetracycline derivatives minocycline (MINO), tigecycline (TIG), and doxycycline (DOX) have also been used in this regard. These latter drugs, like CTX, have broad effects on the gut microbiome (Wong et al., 2016; Ferrer et al., 2017; Hasebe et al., 2019; Schmidtner et al., 2019; Leigh et al., 2020). In general, the tetracyclines are used in studies of drugs of abuse for their anti-inflammatory properties via blockade of microglial activation and inhibition of matrix metallopeptidases, cyclooxygenase-2, protein kinase C, phospholipase A2, and/or nitric oxide synthase (Garrido-Mesa et al., 2013), although these drugs are by no means specific for acting on microglia (Möller et al., 2016). The antibiotic effects of β-lactams and tetracycline derivatives on bacteria in turn can lead to significant alterations in gut microbial activity and gene and protein expression, microbiome metabolite content (long linear and branched-chain fatty acids, saturated and unsaturated fatty acids), branched-chain amino acids, sugars, peptides, and polyamines (Willing et al., 2011; Pérez-Cobas et al., 2013; Becattini et al., 2016; Zhang and Chen, 2019). These alterations in the gut microbiome, many of which are adverse to the host, could then reverberate into the CNS via the gut-brain axis.

A. Antibiotics and Cocaine. A large number of studies have examined CTX for its ability to alter the addictive properties of cocaine. These publications are highlighted in Table 1. The general experimental approach in the majority of these preclinical studies is to establish consistent self-administration of cocaine, which is then extinguished, and CTX is given at the start of cue-primed reinstatement of cocaine self-administration. Some investigators have also used the CPP and the locomotor sensitization models. Most of these studies highlighted in Table 1 document that CTX and other β-lactam antibiotics, such as ampicillin and CLV, indeed decrease reinstatement of cocaine seeking after extinction of self-administration. It has been reported that CTX decreases the reinforcing efficacy of cocaine (Kim et al., 2016). Although some of these studies showed that CTX increased GLT1 expression and function, some did not. None of the studies in Table 1 mentioned the potential effects of CTX-induced alterations in the gut microbiome. Nonetheless, several of these papers do present data that open the results on CTX and cocaine reinstatement to alternative interpretations. One study showed that increases in GLT1 expression using a viral vector harboring the GLT1 construct reduced glutamate efflux but did not block cocaine reinstatement (Logan et al., 2018). Another study showed that amoxicillin reduced cocaine seeking after cue-primed reinstatement without increasing expression of GLT1. CLV did not reduce cocaine seeking under cue-primed reinstatement but did restore GLT1 levels in the NAc versus the cocaine-induced reduction in this protein (Bechard et al., 2019). A third study tested CTX to block cocaine reinstatement in rats trained to self-administer cocaine alone or cocaine plus alcohol (Stennett et al., 2020). These investigators made the interesting observation that CTX attenuated relapse in the cocaine-only group but not in the cocaine + alcohol group, but the latter treatment group showed increased GLT1 expression in the NAc (Stennett et al., 2020). Focus on the GLT1 in mediating CTX-induced prevention of cue-induced relapse to cocaine self-administration has

TABLE 1
Antibiotics and cocaine reward and relapse

Reference	Drug of Abuse	Addiction Model	Antibiotic and Dose	Ab Treatment Duration	Outcome	GLT1/Glia Measured	Gut Microbiome Mentioned or Assessed
Sari et al. (2009)	Cocaine	S/A	CTX (100, 200 mg/kg) CTX (50 mg/kg)	Given after each session of S/A for 5 days	↓ cue-induced REL at 100, 200; no effect of 50	Yes	No
Knackstedt et al. (2010)	Cocaine	S/A, EXT, REL	CTX 200 mg/kg	Last 7 days of 3 wk EXT	↓ cue- and drug-induced REL	Yes	No
Sondheimer and Knackstedt (2011)	Cocaine	S/A, ACQ, REL	CTX 200 mg/kg	5 Days before S/A (10 days) until EXT	No effect on ACQ of S/A; ↓ REL; ↓ LS	Yes	No
Ward et al. (2011)	Cocaine	S/A ACQ, CPP	CTX 100 or 200 mg/kg	3 Days before S/A and continue 10 days of S/A	200 ↓ S/A; 100 did not; no effect on development of CPP	No	No
Trantham-Davidson et al. (2012)	Cocaine	S/A	CTX 200 mg/kg	12 Days during S/A and for last 5 days of EXT 2 to 3 wk	No effect on ACQ or EXT	No	No
Fischer et al. (2013)	Cocaine	S/A	CTX 200 mg/kg	Last 5 days of EXT for 5 or 45 days	↓ REL only in long EXT group	Yes	No
Tallarida et al. (2013)	Cocaine	LS; LA	CTX 200 mg/kg	30 Days of abstinence; 14 days with COC; 10 days prior to 1X COC	↓ LS both durations; ↓ acute COC at high dose COC (30), not low (15)	No	No
Barr et al. (2015)	Cocaine	LA	CTX 200 mg/kg	10 Days	↓ COC increase in LA	No	No
Freet and Lawrence (2015)	Cocaine	↓ saccharin intake	CTX 200 mg/kg	8 Days	↓ ACQ and ↑ EXT of suppression of saccharin intake	No	No
Weiland et al. (2015)	Cocaine	REL	CTX 200 mg/kg, CEF 100 ng/kg	8 Days	↓ REL CEF did not ↓ REL	No	No
Kim et al. (2016)	Cocaine	S/A	CLV 1, 10 mg/kg, CTX 200 mg/kg	7–10 Days 7–10 days	No ↓ of ACQ of S/A; ↓ breakpoint	Yes	No
Garcia-Keller et al. (2016)	Cocaine	Stress ↑ S/A	CTX 200 mg/kg	10 Days (3 before S/A then 7 more during)	↓ stress-induced ↑ in LA and stress-induced ↑ ACQ of S/A	No	No
LaCrosse et al. (2016)	Cocaine	REL S/A	CTX 100 mg/kg, CTX 200 mg/kg	21 Days Ab and CTX during last 6 days	No effect on ACQ of S/A; both CTX doses ↓ REL	Yes	No
Hammad et al. (2017)	Cocaine	REL of CPP	AMP/SUB 200 mg/kg together	200 mg/kg 4 days	AMP/SUB ↓ REL of CPP	Yes	
LaCrosse et al. (2017)	Cocaine	REL of S/A	CTX 200 mg/kg	6 Days	↓ REL with GLT1 antisense knockdown, CTX did not block as much but still has an effect	Yes	No
Bechard et al. (2018)	Cocaine	REL of S/A	CTX 200 mg/kg	Min of 6 days in EXT just before REL	↓ REL in ♂ and ♀; small ↓ REL	Yes	No
Logan et al. (2018)	Cocaine	REL of S/A	Ab not used; viral vector used to ↑ GLT1 levels	–	Vector ↑ GLT1 expression but did not ↓ REL of COC seeking	Yes after viral vector	No
Schwendt et al. (2018)	Cocaine	PTSD + S/A	CTX 200 mg/kg	9 Days during EXT	Rats susceptible to stress show ↓ EXT and ↑ cue-primed REL that is not prevented by CTX. In Con and stress-resistant rats, CTX blocked cue-primed REL	No	No
Bechard et al. (2019)	Cocaine	REL of S/A	AMX 100 mg/kg, CLV 5 mg/kg, AMX (20) + CLV (80)	5 Days in EXT prior to REL test	AMX only ↓ REL; CLV and AUG did not	Yes	No
Bechard and Knackstedt (2019)	Cocaine	REL of S/A	CTX 200 mg/kg	6 Days during EXT outside of S/A context	↓ cue REL and no additive effect of CTX with cue EXT; cue EXT alone did not without CTX also did not ↓ REL as in humans	No	No
Niedzielska-Andres et al. (2019)	Cocaine	CPP	CTX 200 mg/kg	7 Days during drug-free period in home cage	↓ CPP	Yes	No
Stennet et al. (2020)	Cocaine + alcohol	REL of S/A	CTX 200 mg/kg	5–7 Days in EXT prior to REL	↓ REL in COC-only group; CTX does not ↓ COC REL in COC + ALC group	Yes	No
Logan et al. (2020)	Cocaine	REL of S/A	CTX 200 mg/kg	6–10 Days in EXT prior to REL	↓ REL; mGluR2 antagonists in NAc prevented CTX effect	No	No
Chen et al. (2009)	Cocaine	LS	MINO 40 mg/kg	3 h before cocaine on 4 days of LS training	↓ LS	No/No	No

↓, decreases; ↑, increases; ♂, male; ♀, female; Ab, antibiotic; ACQ, acquisition; ALC, alcohol; AMX, amoxicillin; AMP, ampicillin; AUG, Augmentin; CEF, cefazolin; COC, cocaine; Con, control; EXT, extinction; LA, locomotor activity; LS, locomotor sensitization; Min, minimum; PTSD, post traumatic stress disorder; REL, relapse/reinstatement; S/A, self-administration; SUB, suboximine.

shifted somewhat to the metabotropic glutamate receptor 2 (mGluR2) after the demonstration that the mGluR2 antagonist LY341495 injected directly into the NAc prevented CTX from attenuating reinstatement of cocaine seeking (Logan et al., 2020). Finally, cefazolin was found not to reduce cocaine reinstatement (Weiland et al., 2015). MINO prevents the development of cocaine locomotor sensitization (Chen et al., 2009) as is seen with CTX (Sondheimer and Knackstedt, 2011).

B. Antibiotics and Alcohol. CTX has been used in studies with alcohol to increase GLT1 expression in the same manner used to reduce cocaine reward. Most studies examining the effects of CTX on alcohol have used alcohol-preferring rats that are exposed to voluntary alcohol drinking for times ranging from 5 to 14 weeks. Thereafter, CTX (or another antibiotic) is given for 5–7 days in the first or second week after chronic drinking, and intake is measured for the remainder of the experiment. This approach is referred to as relapse-like drinking and has been used effectively by Sari and colleagues. Publications reporting alcohol-antibiotic interactions are highlighted in Table 2. The literature is in good agreement in showing that CTX reduces relapse-like drinking (Sari et al., 2011, 2013a,b, 2016; Qrunfleh et al., 2013; Alhaddad et al., 2014; Rao and Sari, 2014a,b; Das et al., 2015; Rao et al., 2015c; Stennett et al., 2017). Ampicillin, cefazolin, cefoperazone, CLV, amoxicillin, and Augmentin share with CTX the ability to reduce relapse-like drinking (Goodwani et al., 2015; Hakami et al., 2017; Hakami and Sari, 2017; Rao et al., 2015b). In addition, CTX blocks acquisition of alcohol intake (Sari et al., 2013a) and attenuates alcohol withdrawal syndrome (Abulseoud et al., 2014). CTX and cefazolin also attenuate cue-primed reinstatement of alcohol drinking using an operant approach (Weiland et al., 2015). The majority of the studies referenced in Table 2 confirmed antibiotic-induced increases in expression of GLT1, with some interesting exceptions (see below). A smaller number of studies have tested various tetracycline derivatives, and despite the fact that these drugs were used for their ability to block microglial activation and reduce neuroinflammation, none of these effects were documented. When given before alcohol, MINO, TIG, and DOX significantly reduce voluntary drinking (Agrawal et al., 2011; Bergeson et al., 2016; Syapin et al., 2016). MINO also blocks alcohol reward as assessed by CPP (Gajbhiye et al., 2017), and both MINO and TIG reduce alcohol withdrawal (Martinez et al., 2016; Gajbhiye et al., 2018). A number of reviews have been published on CTX-GLT1–alcohol dependence interactions (Rao and Sari, 2012; Sari, 2013; Rao et al., 2015a; Bell et al., 2017).

C. Antibiotics and Opiates. A relatively small number of studies have investigated the interactions between antibiotics and opiates, and these papers are highlighted in Table 3. Early studies established that CTX attenuates morphine dependence, analgesic tolerance, and precipitated withdrawal (Rawls et al., 2010a,b; Habibi-Asl et al., 2014) and inhibits the development of morphine hyperalgesia (Chen et al., 2012). Other investigations determined that CTX and CLV decreased acquisition and/or reinstatement of a morphine (Schroeder et al., 2014; Mehri et al., 2018) or hydrocodone CPP (Alshehri et al., 2018), whereas another study reported that CTX alone did not alter acquisition and reinstatement of a morphine CPP (Fan et al., 2012). Finally, it has been reported that CTX prevented cue-induced heroin seeking (Shen et al., 2014). Most of these studies did not confirm altered expression of GLT1, but the paper of Shen et al. (2014) did provide an extensive investigation of *N*-methyl-d-aspartate receptor electrophysiology that documented increased glutamate uptake after CTX treatment. One study did establish CTX-mediated increases in GLT1 expression (Chen et al., 2012), and another reported that CTX decreased reinstatement of an opiate CPP without increasing GLT1 expression (Alshehri et al., 2018). MINO has been shown to decrease (Hutchinson et al., 2008) and facilitate extinction and reduce reinstatement of the morphine CPP (Arezoomandan and Haghparast, 2016). MINO also delays the development of morphine analgesic tolerance but does not reverse existing tolerance in rats with neuropathic pain (Zhang et al., 2015).

D. Antibiotics and Methamphetamine, Amphetamine, and Nicotine. A few of studies have investigated the effects of antibiotics on dependence-like behaviors associated with methamphetamine, amphetamine, and nicotine, and these are highlighted in Table 4. Both CTX (Abulseoud et al., 2012) and CLV (Althobaiti et al., 2019) reduce reinstatement of the extinguished methamphetamine CPP. CTX also reduces cue-primed reinstatement of amphetamine self-administration (Garcia et al., 2019) and decreases amphetamine-induced behavioral sensitization (Rasmussen et al., 2011). MINO reduces the formation and reinstatement of a methamphetamine CPP (Fujita et al., 2012; Attarzadeh-Yazdi et al., 2014) and also reduces methamphetamine self-administration (Snider et al., 2013). In humans, MINO reduces the subjective effects of amphetamine but does not alter amphetamine choice (Sofuoglu et al., 2011). With regard to nicotine, CTX reduces the development of nicotine analgesic tolerance (Schroeder et al., 2011), attenuates the persistence of a nicotine CPP (Philogene-Khalid et al., 2017), and reduces its reinstatement (Alajaji et al., 2013). Finally, MINO has been shown to reduce craving for cigarettes in humans, but it does not alter smoking self-administration or the subjective responses to intravenous nicotine (Sofuoglu et al., 2009).

E. Summary and Alternative Interpretations of Studies Examining Effects of Antibiotics on the Rewarding Effects of Drugs of Abuse. The interpretation

TABLE 2
Antibiotics and alcohol drinking and reward

Reference	Drug of Abuse	Addiction Model	Antibiotic and Dose	Ab Treatment Duration	Outcome	GLT1/Glia Measured	Gut Microbiome Mentioned or Assessed
Sari et al. (2011)	Alcohol	AD in ALC-P rats	CTX 25, 50, 100, 200 mg/kg	7 wk ALC ACQ then CTX for 5 days in wk 6, measure AD to end	Most doses ↓ AD gradually; rats had prior 7 wk exposure to AD then 2 wk WD	Yes	No
Qrunfleh et al. (2013)	Alcohol	REL to AD in ALC-P rats	CTX 50, 100 mg/kg	5 wk ALC ACQ 2 wk off ALC; CTX for 5 days in wk 6, measure AD to end	Both doses ↓ AD; 50 dose ↓ intake but did not ↑ GLT1	Yes	No
Sari et al. (2013a)	Alcohol	ACQ of AD in ALC-P rats	CTX 200 mg/kg	7 Days then ALC ACQ, then 7 days CTX ALC maintenance	CTX no/slight effect on ACQ; CTX reduced AD	Yes	No
Sari et al. (2013b)	Alcohol	AD in ALC-P rats	CTX 100 mg/kg	5 wk ALC 5 days CTX, AD 8 days	CTX ↓ AD throughout 8 days	Yes	No
Rao and Sari (2014a)	Alcohol	AD in ALC-P rats	CTX 100 mg/kg	14 wk AD; 5 days CTX; AD 10 days more	CTX ↓ AD over 10 days, but effect diminished at end	Yes	No
Rao and Sari (2014b)	Alcohol	REL to AD in ALC-P rats	CTX 50 or 200 mg/kg	14 wk AD; 2 wk WD; CTX during last 5 days of WD, measure AD 10 days	CTX 100 ↓ AD, but 50 dose did not	No	No
Alhaddad et al. (2014)	Alcohol	AD in ALC-P rats	CTX 100 mg/kg	5 wk ALC; 2 wk WD; CTX last 5 days of WD; measure AD 9 days	CTX ↓ REL to AD	Yes	No
Abulseoud et al. (2014)	Alcohol	ALC WD in ALC-P and Wistar rats	CTX 100 or 200 mg/kg	2 wk AD (free, gavage 3–5 days); 48 h WD CTX during WD	CTX ↓ WD signs; when ALC reintroduced after WD, CTX ↓ REL to AD	Yes	No
Weiland et al. (2015)	Alcohol	REL to AD	CTX 200 mg/kg, CEF 100 mg/kg, NAC 60 mg/kg	Last 6–8 days of 10 days WD	CTX and CEF ↓ REL of AD; NAC had no effect	No	No
Rao et al. (2015c)	Alcohol	AD in ALC-P rats	CTX 100 mg/kg	5 wk AD; CTX 2 or 5 days	CTX ↓ AD for 2 and 5 days CTX admin	Yes	No
Rao et al. (2015b)	Alcohol	AD in ALC-P rats	AMP, CEF, CEFO all 100 mg/kg	5 wk AD; 5 days in wk 6; measure AD to end	All ↓ AD	Yes	No
Goodwani et al. (2015)	Alcohol	AD in ALC-P rats	AMOX 100 mg/kg AMOX/CLV 100 mg/kg	5 wk AD; AMOX or AUG 5 days in wk 6	AMOX and AUG ↓ AD	Yes	No
Das et al. (2015)	Alcohol	AD in ALC-P rats	CTX 100 mg/kg	5 wk AD; CTX 5 days in wk 6; measure AD to end	CTX ↓ AD	Yes	No
Sari et al. (2016)	Alcohol	AD in ALC-P rats	CTX 200 mg/kg	5 wk AD; CTX 7 days through 5th wk of AD	CTX ↓ AD in wk 5	Yes	No
Hakami and Sari (2017)	Alcohol	AD in ALC-P rats	CLV 5 mg/kg	5 wk AD, CLV for 5 days in wk 6, measure AD to end	CLV ↓ AD through wk 6	Yes	No
Stennett et al. (2017)	Alcohol	AD	CTX 200 mg/kg	17 Days AD; CTX 5 days	CTX ↓ AD	Yes	No
Hakami et al. (2017)	Alcohol	AD in ALC-P rats	AUG 100 mg/kg	5 wk AD; AUG 5 days in wk 6 through end	AUG ↓ AD on all 5 days	Yes	No
Agrawal et al. (2011)	Alcohol	AD	MINO 50 mg/kg 1× before AD	Just before AD	MINO small ↓ AD; MINO also ↓ water intake in ♂ rats	No/No	No
Bergeson et al. (2016)	Alcohol	AD in dependent and nondependent mice	TIG 40, 60, 80, or 100 mg/kg	1 h pre-ALC	Only 80 and 100 mg/kg doses ↓ AD in dependent and nondependent mice	No	Yes
Syapin et al. (2016)	Alcohol	AD	Seven tetracyclines; all at 50 mg/kg	20 h before first ALC exposure then 1/day for 4 days	MINO > DOX > TIG in ↓ AD	No	No
Martinez et al. (2016)	Alcohol	ALC WD	TIG 20, 40, 80 mg/kg	Concurrent with ALC or 4 or 7 h after for highest dose	TIG ↓ WD signs and ALC convulsions in dose-related manner	No	No
Gajbhiye et al. (2017)	Alcohol	ALC REL of CPP	MINO 10, 30, 50 mg/kg	30 min prior to each of four ALC injections	MINO ↓ ALC CPP and blocked REL to CPP	No/No	No
Gajbhiye et al. (2018)	Alcohol	ALC WD anxiety and REL	MINO 5, 10, 20 mg/kg	Acute before ALC	MINO ↓ WD anxiety and REL to AD	No/No	No

↓, decreases; ↑, increases; ♂, male; Ab, antibiotic; ACQ, acquisition; AD, alcohol drinking; ALC, alcohol; ALC-P, alcohol-preferring rats; AMOX, amoxicillin; AMP, ampicillin; AUG, Augmentin; CEF, cefazolin; CEFO, cefoperazone; NAC, N-acetylcysteine; REL, relapse/reinstatement; WD, withdrawal.

of results from the vast majority of studies of antibiotic interactions with drugs of abuse focuses on β-lactams for the ability to increase expression of GLT1 and on tetracyclines for their ability to reduce microglial activation and neuroinflammation. Often, neither of these purported effects was confirmed. However, the outcomes of the studies in this section leave open the possibility that the gut microbiome is involved in antibiotic-induced reward reduction for the following reasons:

1. All drugs of abuse considered in the foregoing section cause significant disruptions in the gut microbiome.
2. CTX can increase expression of the GLT1, but MINO does not, yet both can alter the rewarding effects of drugs of abuse. Although CTX and MINO may influence drug reward via different CNS actions, both have antimicrobial properties and effects that have not been considered in data interpretation. In fact, the common property shared by all antibiotics discussed above is the ability to knock down the gut microbiome. Even CLV, which retains the β-lactam moiety required to increase GLT1 expression but reportedly has minimal antimicrobial activity, does indeed have antibacterial actions (Finlay et al., 2003; Ferrer et al., 2017). Therefore, all antibiotics alter the gut microbiome, and their varying effects on the rewarding properties of drugs of abuse may be explained by the specific pattern by which they do so. It is also significant that antibiotics are administered on a background of drug-induced disturbances in the gut microbiome. The possibility of gut microbiome involvement in the actions of antibiotics was acknowledged by only one study highlighted in Table 2. Although the study by Bergeson et al. (2016) showed TIG-mediated reduction in alcohol intake, a role for the gut microbiome was discounted because of the short duration of antibiotic treatment (1 hour prior to alcohol), and a mechanism was not posited to explain this antibiotic-induced reduction of alcohol intake.
3. Assuming that CTX-induced increases in GLT1 expression are the mechanism by which drug reward is blocked, a significant dissociation exists between GLT1 expression and reward reduction. This discrepancy exists in studies of cocaine (Logan et al., 2018; Bechard et al., 2019; Stennett et al., 2020), wherein antibiotics may or may not alter GLT1 expression and/or cocaine reward. With regard to alcohol, Qrunfleh et al. (2013) showed that although CTX doses of 50 and 100 mg/kg both significantly reduced relapse-like drinking of alcohol, only the higher dose increased GLT1 levels. Rao et al. (2015c) treated alcohol-preferring rats with CTX (100 mg/kg) for 2 or 5 days after a 5-week period of voluntary drinking and found that although CTX reduced drinking at both times, GLT1 expression was only increased significantly at the 5-day time point. In addition, Stennett et al. (2017) showed that CTX (200 mg/kg for 2 or 5 days) decreases alcohol consumption without changing GLT1 expression in the NAc. The morphine CPP and the development of locomotor sensitization are reduced by CLV (Schroeder et al., 2014) without evidence of altered GLT1 expression. CTX and CLV both block reinstatement of the methamphetamine CPP, but their effects on GLT1 expression differ substantially—CLV increased GLT1 expression (Althobaiti et al., 2019), whereas CTX did not (Abulseoud et al., 2012). Finally, and most importantly, Knackstedt and colleagues have shown conclusively that increased expression of GLT1 is not the mechanism by which antibiotics reduce cocaine reward (Logan et al., 2018; Bechard et al., 2019; Stennett et al., 2020). More recent studies have focused on CTX- and cocaine-induced alterations in the mGluR2 versus the GLT1 (Logan et al., 2020). Logan et al. (2020) demonstrated that CTX attenuates reinstatement of cocaine self-administration, and a Glu2 receptor antagonist injected directly into the NAc blocks the effect of CTX.
4. Most studies highlighted in Tables 1–4 administered high doses of CTX (200 mg/kg is the most common dose) for 5–12 days prior to tests of reinstatement, a course of treatment known to significantly alter the composition of the gut microbiome in humans (Burdet et al., 2019) and animals alike (Luo et al., 2016; Connelly et al., 2017; Chakraborty et al., 2018; Luo et al., 2018; Holota et al., 2019; Miao et al., 2020). It is also interesting that the original report on CTX-mediated neuroprotection used the same course of treatment in the G93A-SOD1 mouse model of amyotrophic lateral sclerosis (Rothstein et al., 2005), a mouse that is now known to have a leaky intestine and an impaired gut microbiome (Wu et al., 2015). Therefore, high-dose antibiotic treatment would impart an additional dysbiotic effect on a gut microbiome already substantially altered by drugs of abuse.
5. Antibiotic interference with the rewarding effects of drugs of abuse is partial. When the gut microbiome is given more consideration in studies of drug reward, it should be possible to use different and more-specific antibiotics as well as other well known and validated approaches to alter the gut microbiome to more completely prevent the rewarding effects of drugs of abuse.

TABLE 3
Antibiotics and opiate tolerance, withdrawal, and reward

Reference	Drug of Abuse	Addiction Model	Antibiotic and Dose	Ab Treatment Duration	Outcome	GLT1/Glia Measured	Gut Microbiome Mentioned or Assessed
Rawls et al. (2010a)	Morphine	MD	CTX 50, 100, 150, 200 mg/kg	2 Days before MOR and with MOR for another 10 days	CTX (150 and 200 mg/kg) ↓ induced WD	No	No
Rawls et al. (2010b)	Morphine	Analgesic TOL	CTX 25, 50, 100 mg/kg	3 Days before MOR and with MOR for another 7 days	CTX (50 and 100 mg/kg) ↓ development of analgesic TOL	No	No
Chen et al. (2012)	Morphine	Hyperalgesia	CTX 200 mg/kg	3 Days before MOR and with MOR for another 4 days	CTX ↓ hyperalgesia	Yes	No
Fan et al. (2012)	Morphine	CPP	CTX 25 mg/kg	Before MOR on each day	CTX alone did not alter any facet of CPP; CTX + MK-801 (NMDAR antagonist) reduced ACQ of CPP and ↓ REL to CPP	No	No
Shen et al. (2014)	Heroin	S/A	CTX 200 mg/kg	Start on day 8 of EXT and for 7 days more	CTX ↓ cue-induced REL	No but confirmed with electrophys	No
Habibi-Asl et al. (2014)	Morphine	MD and TOL	CTX 50, 100, 200 mg/kg	4 Days before MOR	CTX ↓ analgesic TOL and ↓ naloxone WD	No	
Schroeder et al. (2014)	Morphine	CPP, hyperthermia, LS	CTX 200 mg/kg, CLV 10 mg/kg	3 Days before and through conditioning	CTX and CLV ↓ CPP, hyperthermia, and LS	No	No
Alshehri et al. (2018)	Hydrocodone	CPP in ALC-P rats	CTX 200 mg/kg	CTX every other day for days 14–21 in EXT	CTX ↓ REL	Yes	No
Mehri et al. (2018)	Morphine	CPP	CLV 1, 50, 150 mg/kg	With MOR 4 days in conditioning phase	CLV (50 and 150 mg/kg) ↓ ACQ of CPP and ↓ REL	No	No
Hutchinson et al. (2008)	Morphine	Respiratory depression, CPP	MINO 25 or 50 mg/kg 30 min before MOR	Before MOR and throughout	MINO 50 mg/kg ↓ CPP	No/no	No
Zhang et al. (2015)	Morphine	Analgesic TOL in rats with spinal nerve ligation	MINO 30 mg/kg	Start at day 7 for 3 days before MOR	MINO ↓ development of TOL	No/no	No
Arezoomandan and Haghparast (2016)	Morphine	CPP	MINO 1, 5, 10 ug into NAc each of 7 days of EXT	Before MOR on each of 7 days of EXT	MINO ↑ EXT of CPP and ↓ REL	No/no	No

↓, decreases; ↑, increases; Ab, antibiotic; ACQ, acquisition; ALC-P, alcohol-preferring rats; electrophys, electrophysiology; EXT, extinction; LS, locomotor sensitization; MD, morphine dependence; MOR, morphine; NMDAR, NMDA receptor; REL, relapse/reinstatement; S/A, self-administration; TOL, tolerance; WD, withdrawal.

TABLE 4
Antibiotics and methamphetamine, amphetamine, and nicotine reward

Reference	Drug of Abuse	Addiction Model	Antibiotic and Dose	Ab Treatment Duration	Outcome	GLT1/Glia Measured	Gut Microbiome Mentioned or Assessed
Abulseoud et al. (2012)	Methamphetamine	CPP	CTX 200 mg/kg	1/Day for 7 days of EXT	CTX ↓ REL of CPP	Yes	No
Althobaiti et al. (2019)	Methamphetamine	CPP in ALC-P rats exposed to ALC	CLV 5 mg/kg	1/Day for 7 days of EXT	CLV ↓ REL of CPP	Yes	No
Rasmussen et al. (2011)	Amphetamine	LS	CTX 200 mg/kg	1/Day for 8 days	CTX ↓ LS	No	No
Garcia et al. (2019)	Amphetamine	S/A	CTX 200 mg/kg	1/Day for 10 days in EXT	CTX ↓ S/A in enriched housing rats and ↓ drug-cued REL	Yes	No
Fujita et al. (2012)	Methamphetamine	CPP	MINO 40 mg/kg	1/Day for 6 days in conditioning	MINO ↓ CPP	No/no	No
Snider et al. (2013)	Methamphetamine	S/A	MINO 10, 30, 60 mg/kg	1/Day for 3 days during S/A	MINO only at 60 mg/kg ↓ S/A	No/no	No
Attarzadeh-Yazdi et al. (2014)	Methamphetamine	CPP	MINO 40 mg/kg	1/Day for 9 to 10 days of EXT	MINO ↓ CPP and ↓ drug-primed REL	No/no	No
Sofuoglu et al. (2011)	Amphetamine	Human subjective scores and choice for S/A	MINO 200 mg/day	4 Days	MINO ↓ subjective rewarding effects but did not change choice	No/no	No
Schroeder et al. (2011)	Nicotine	Analgesic TOL	CTX 200 mg/kg	1/Day for 5 days before and throughout analgesic testing 1–7 days	CTX ↑ analgesia and ↓ analgesic TOL	No	No
Philogene-Khalid et al. (2017)	Nicotine	CPP	CTX 200 mg/kg	1/Day for 7 days post-testing	CTX ↓ CPP persistence	No	No
Sofuoglu et al. (2009)	Nicotine	Smoking S/A, craving in humans	MINO 200 mg/day	1/Day for 4 days	MINO ↓ craving but did not alter smoking or responses to iv nicotine	No/no	No

↓, decreases; ↑, increases; Ab, antibiotic; ACQ, acquisition; ALC, alcohol; ALC-P, alcohol-preferring rats; EXT, extinction; iv, intravenous; LS, locomotor sensitization; REL, relapse/reinstatement; S/A, self-administration; TOL, tolerance.

Taken together, abundant evidence exists implicating the gut microbiome in the mechanism by which antibiotics alter the rewarding effects of drugs of abuse. A role for the gut microbiome is rarely considered, but the disparities in outcomes described above justify a much more comprehensive analysis of how the gut microbiome can influence drug reward.

IV. Sodium Butyrate, Histone Deacetylase Enzymes, and Drugs of Abuse

The intended use of NaB in modifying the dependence-like actions of drugs of abuse has been strictly as an inhibitor of histone deacetylase (HDAC) enzymes, which is an effect first demonstrated by Candido et al. (1978) in cultured cells. HDACs catalyze the removal of acetyl groups from lysine residues in histone proteins, an epigenetic modification that regulates chromatin structure and gene transcription (Seto and Yoshida, 2014). NaB is a weak inhibitor of class I (HDACs 1, 2, 3, and 8) and class IIa (HDACs 4, 5, 7, and 9) HDACs (Eckschlager et al., 2017). Broadly speaking, drugs of abuse can modulate gene transcription and expression via epigenetic mechanisms (Nestler, 2014; Cadet, 2016; Ajonijebu et al., 2017) such that chronic use leads to histone hypoacetylation via the action of HDACs. Therefore, HDAC inhibitors would block deacetylation, restoring gene transcription and expression to normal levels and preventing the transition to or reinstatement of drug use to the level of dependence. However, NaB has many pharmacological actions that go well beyond inhibition of HDACs as recently reviewed (Seto and Yoshida, 2014; Stilling et al., 2016; Dalile et al., 2019; Silva et al., 2020), and these can cloud interpretation of results when it is tested against the actions of drugs of abuse. Specifically, NaB can strengthen cocaine-associated contextual memory (Itzhak et al., 2013), trigger a stress response (Gagliano et al., 2014), and inhibit microglial activation (Huuskonen et al., 2004; Yamawaki et al., 2018), all of which could also modify the effects of drugs of abuse. In addition, the in vivo pharmacokinetics of NaB are such that it achieves very low bioavailability. Kim et al. (2013) found brain uptake of butyrate to be less than 0.006% after intravenous injections of radiolabeled butyrate in primates, leading Stilling et al. (2016) to conclude that it is unlikely that butyrate enters the brain in high enough concentrations to cause direct inhibition of HDACs.

With regard to the gut microbiome, butyric acid is a short-chain fatty acid (SCFA) that is synthesized during anaerobic microbial fermentation of polysaccharides, which cannot be digested by the host. Most butyrate-producing bacteria are found in phylum Firmicutes. Butyric acid can also be obtained from the diet (Stilling et al., 2016). From a pharmacological perspective, the sodium salt of butyric acid, NaB, is the form used almost exclusively in studies aimed at modifying the actions of drugs of abuse. The administration of exogenous NaB modifies the gut microbiome (Zhou et al., 2017; Fang et al., 2019; Yu et al., 2019), so this could represent another mechanism by which it alters drug reward. Another emerging mechanism by which NaB could alter the actions of drugs of abuse via the gut-brain axis involves ghrelin signaling. Ghrelin is a 28-amino-acid peptide that is secreted by A-like–type cells of the stomach (Sakata and Sakai, 2010). Ghrelin signaling is mediated by the growth hormone secretagogue receptor 1a (GHSR1a), which is expressed in brain and modulates the appetite-inducing effects of ghrelin (Sakata and Sakai, 2010). It has been shown recently that butyrate and other SCFAs decrease ghrelin signaling by blocking GHSR1a (Torres-Fuentes et al., 2019). This is highly relevant to SUDs because ghrelin administration can increase alcohol intake and enhance preference for cocaine, whereas GHSR1a antagonists and GHSR1a gene knockouts show reduced voluntary intake of alcohol, stimulants, and nicotine, as reviewed recently (Panagopoulos and Ralevski, 2014; Zallar et al., 2017).

A. Sodium Butyrate and Cocaine. The literature on NaB-induced modification of cocaine actions is somewhat variable, and these studies are highlighted in Table 5. Most of these studies verified histone acetylation levels and/or changes in gene expression, but none included the gut microbiome in the interpretation of results. NaB decreases cocaine reward and increases cocaine extinction and reinstatement. NaB has been shown to increase cocaine self-administration (Sun et al., 2008), whereas phenylbutyrate, which is also used as an HDAC inhibitor, decreases self-administration and decreases motivation for cocaine (Romieu et al., 2008, 2011). In the CPP model of cocaine reward, NaB increases acquisition of a cocaine CPP (Raybuck et al., 2013) and decreases reinstatement of the extinguished CPP (Malvaez et al., 2010). Lower doses of NaB (300–600 mg/kg) increase extinction of the cocaine CPP (Raybuck et al., 2013), whereas the higher dose of 1200 mg/kg can either increase (Malvaez et al., 2013) or decrease (Raybuck et al., 2013) extinction of the cocaine CPP. NaB does not modify the DA D_1 receptor (DA D_1R) agonist–induced increase in a cocaine CPP (Schroeder et al., 2008). Finally, NaB increases the locomotor sensitization caused by cocaine (Sanchis-Segura et al., 2009) and cocaine plus a D1 agonist (Schroeder et al., 2008), suggesting enhancement of cocaine-induced reward. On the other hand, HDAC inhibitors other than NaB have fairly consistent effects on cocaine reward. For instance, the pan-HDAC inhibitor tricostatin A decreases cocaine self-administration (Romieu et al., 2008; Host et al., 2010; Romieu et al., 2011). The specific HDAC3 inhibitor RGFP966 increases extinction of the cocaine CPP (Malvaez et al., 2013) and increases extinction of cocaine self-administration and decreases its reinstatement (Hitchcock et al., 2019). The class I HDAC inhibitor

MS-275 decreases cocaine locomotor sensitization (Kennedy et al., 2013). In contrast, the class II HDAC inhibitor MC1568 enhances cocaine self-administration (Griffin et al., 2017). These latter results add some substantiation to the conclusion that HDAC inhibition can alter cocaine actions. The roles played by epigenetics by cocaine have been reviewed (Kreek et al., 2012; Cadet, 2016).

B. Sodium Butyrate and Alcohol. A small number of studies have investigated the effects of NaB on alcohol drinking and reward, and these are highlighted in Table 5. The effects of NaB on histone acetylation levels and/or alterations in gene expression were verified in all. The gut microbiome was not considered in the interpretation of the data of any. It can be seen in Table 5 that NaB can either increase (Sanchis-Segura et al., 2009) or decrease (Legastelois et al., 2013) alcohol-induced locomotor sensitization. NaB increases acquisition of an alcohol CPP (Xu et al., 2012) but decreases alcohol drinking in dependent rats and prevents escalation to excessive drinking (Simon-O'Brien et al., 2015). The HDAC class I–specific inhibitor MS-275 reduces alcohol self-administration and decreases relapse (Jeanblanc et al., 2015). Valproic acid, a short branched-chain fatty acid derived from the SCFA valeric acid and an inhibitor of class I and IIA HDACs, lowers preference for alcohol and reduces consumption in the two-bottle choice paradigm, and it blocks formation of an alcohol CPP (Al Ameri et al., 2014). For the most part, the studies of NaB and alcohol are inconsistent, as is the case for cocaine, showing increases or decreases in alcohol dependence and reward. Nevertheless, all studies in Table 5 attributed the effects of NaB on alcohol reward to decreases in HDAC activity and/or epigenetic alterations. The role of HDAC inhibition and epigenetic alterations in alcohol reward and drinking has been reviewed (Palmisano and Pandey, 2017; Pandey et al., 2017; Ponomarev et al., 2017).

C. Sodium Butyrate and Opiates. The studies investigating NaB-opiate interactions are also highlighted in Table 5. The majority of these studies confirmed NaB-induced alterations in histone acetylation and/or gene expression, and none included discussion of the gut microbiome in the interpretation of results. Using the CPP model of drug reward, it has been shown that NaB increases the development of a morphine CPP (Sanchis-Segura et al., 2009) while increasing CPP extinction and reducing reinstatement (Wang et al., 2010). NaB has been shown to increase the development of locomotor sensitization (Sanchis-Segura et al., 2009), although it and valproic acid given separately decrease sensitization (Jing et al., 2011). Heroin self-administration is not altered by NaB, and this HDAC inhibitor increases reinstatement of heroin-primed self-administration (Chen et al., 2016). Finally, the genetic deletion of the *Per1* clock gene impairs the development of morphine-induced sensitization and the CPP (Perreau-Lenz et al., 2017). Interestingly, these mice show significant increases in global levels of histone acetylation. Treatment of the Per1 knockout mice with NaB restores development of both morphine sensitization and CPP (Perreau-Lenz et al., 2017). In general, it is difficult to attribute NaB-induced alterations in the rewarding effects of opiates to HDAC inhibition because NaB can increase or decrease dependence-like behavior. NaB has no effect on opiate self-administration but can increase primed reinstatement of morphine self-administration, implying that HDAC inhibition increases seeking behavior for opiate reward. The role of HDAC inhibition and/or epigenetic alterations in opiate reward has been the subject of several review articles (Kreek et al., 2012; Browne et al., 2020).

D. Sodium Butyrate and Methamphetamine, Amphetamine, and Nicotine. NaB and other HDAC inhibitors have been tested with methamphetamine, amphetamine, and nicotine in a small number of studies, and these are highlighted in Table 5. NaB increases (Harkness et al., 2013), whereas valproic acid decreases (Coccurello et al., 2007), methamphetamine-induced locomotor sensitization. NaB has very complex effects on methamphetamine CPP in that it increases acquisition, increases extinction, and decreases reinstatement (Zhu et al., 2017). The effects of HDAC inhibitors on amphetamine-induced locomotor sensitization are equally confusing. The same investigators showed that NaB and valproic acid could decrease amphetamine sensitization (Kalda et al., 2007) and later reported that both HDACs increased it (Shen et al., 2008). NaB decreases reinstatement of nicotine self-administration only if given immediately after extinction but not if given a few hours later (Castino et al., 2015). Finally, phenylbutyrate decreases the nicotine-induced CPP (Pastor et al., 2011). The role of HDAC inhibition and/or epigenetic alterations in at least methamphetamine reward has been the subject of several review articles (Cadet and Jayanthi, 2013; Godino et al., 2015; Cadet, 2016).

E. Summary and Alternative Interpretations of Studies Examining Effects of Sodium Butyrate on the Rewarding Effects of Drugs of Abuse. Studies investigating the effects of NaB on the rewarding effects of drugs of abuse (see Table 5) attributed the outcomes to NaB-induced alterations in histone acetylation, chromatin remodeling, or epigenetic alterations. However, the outcomes of the studies in this section, as seen above for antibiotics, leave open the possibility that the gut microbiome is involved in NaB-induced reward reduction for the following reasons:

1. Several factors related to the pharmacology of NaB, including the nonselective actions of high dose NaB, the conflicting effects of NaB and other HDAC inhibitors on drug reward

TABLE 5
NaB effects on cocaine, alcohol, opiate, methamphetamine, amphetamine, and nicotine reward and relapse

Reference	Drug of Abuse	Addiction Model	HDAC Inhibitor and Dose	Treatment Duration	Outcome	HDAC Measured	Gut Microbiome Mentioned or Assessed
Sun et al. (2008)	Cocaine	S/A	NaB 100, 200, 400 mg/kg	12 h before coc test	Low doses no effect. Highest dose ↑ S/A	No	No
Schroeder et al. (2008)	Cocaine	CPP	NaB 25 or 100 mg/kg	1/Day for 10 days	NaB ↑ effects of DA D_1R agonist on locomotor; NaB did not enhance DA D_1R effect on CPP	Yes	No
Romieu et al. (2008)	Cocaine	S/A	Phenylbutyrate 20 or 100 mg/kg	30 min before test	Phenylbutyrate ↓ S/A and ↓ breaking point	No	No
Sanchis-Segura et al. (2009)	Cocaine	LS	NaB 100, 150, 300 mg/kg	20 min before test	NaB ↑ LS	Yes	No
Malvaez et al. (2010)	Cocaine	CPP	NaB 1200 mg/kg	During EXT	NaB ↑ CPP EXT; ↓ REL of extinguished CPP	Yes	No
Romieu et al. (2011)	Cocaine	S/A	Phenylbutyrate 20 or 100 mg/kg	1/Day for 5 days	Phenylbutyrate ↓ in S/A	No	No
Raybuck et al. (2013)	Cocaine	CPP	NaB 300, 600, 1200 mg/kg	24 h after conditioning	Highest dose ↑ ACQ of CPP; low dose ↑ EXT; high dose ↓ EXT	Yes	No
Sanchis-Segura et al. (2009)	Alcohol	LS	NaB 100, 150, 300 mg/kg	20 min before test	NaB ↑ LS; does not block TOL to locomotor effects	Yes	No
Xu et al. (2012)	Alcohol	CPP	NaB 200 mg/kg, 4/day for 15 days	Prior to entering chamber	NaB ↑ ACQ of CPP	Yes	No
Legastelois et al. (2013)	Alcohol	LS	NaB 200 or 600 mg/kg	1/Day before alcohol after 30 min, then into LS chamber	NaB ↓ LS, depends on alcohol dose; both 1 and 2 g/kg ↑ LS but NaB only ↓ alcohol dose of 1 g/kg	Yes	No
Simon-O'Brien et al. (2015)	Alcohol	S/A	NaB 600 mg/kg, MS-275 10 mg/kg	30 min before alcohol drinking test	Both ↓ AD in dependent rats, prevented escalation to excessive drinking	Yes	No
Sanchis-Segura et al. (2009)	Morphine	LS and CPP	NaB 100, 150, 300 mg/kg	20 min before testing	NaB ↑ LS; NaB ↑ CPP	Yes	No
Wang et al. (2010)	Morphine	CPP	NaB 1200 mg/kg		NaB ↑ CPP EXT; NaB ↓ REL	No	No
Jing et al. (2011)	Morphine	LS	NaB 40, 80, 160 mg/kg VAL 37.5, 75, 150 mg/kg	1/Day for 3 days 20 min before testing	NaB and VAL ↓ LS	No	No
Chen et al. (2016)	Heroin	S/A	NaB 200, 400 mg/kg	6 h and 12 h before testing	NaB did not alter S/A; NaB ↑ REL of S/A	Yes	No
Perreau-Lenz et al. (2017)	Morphine	LS and CPP in Per1 KO mice (clock gene)	NaB 150 mg/kg	Prior to testing	Per1 KO mice show ↓ of LS and CPP; NaB ↑ LS and CPP in Per1 KO mice	Yes	No
Harkness et al. (2013)	Methamphetamine	LS	NaB 630 mg/kg	30 min prior to each methamphetamine injection	NaB ↑ locomotor response in untreated and sensitized animals; NaB ↑ LS	Yes	No
Zhu et al. (2017)	Methamphetamine	CPP	NaB 400 mg/kg	30 min before methamphetamine	NaB ↑ ACQ of CPP; NaB ↑ EXT of CPP; NaB ↓ REL of CPP	No	No
Coccurello et al. (2007)	Methamphetamine	LS	VAL 150 mg/kg	20 min before methamphetamine	VAL ↓ LS	No	No
Kalda et al. (2007)	Amphetamine	LS	NaB 630 mg/kg, VAL 175 mg/kg	15 min before amphetamine for 6 days	NaB and VAL ↓ LS	Yes	No
Shen et al. (2008)	Amphetamine	LS	NaB 630 mg/kg, VAL 175 mg/kg	15 min before amphetamine	NaB and VAL ↑ LS	Yes	No
Pastor et al. (2011)	Nicotine	CPP	Phenylbutyrate 100 mg/kg	30 min prior to nicotine	Phenylbutyrate ↓ CPP	Yes	No
Castino et al. (2015)	Nicotine	S/A	NaB 100 mg/kg	Immediately or 6 h after EXT sessions	NaB immediate ↓ REL	No	No

↓, decreases; ↑, increases; ACQ, acquisition; AD, alcohol drinking; coc, cocaine; EXT, extinction; KO, knockout; LS, locomotor sensitization; min, minutes; REL, relapse/reinstatement; S/A, self-administration; TOL, tolerance; VAL, valproic acid.

(some increase, some decrease) and the lack of correlation between levels of histone acetylation, and the effect of HDAC inhibitors on reward reduction, temper the conclusions on HDAC involvement.
2. Butyrate is produced endogenously by bacterial fermentation, and when given exogenously, it can cause alterations in the gut microbiome. It does not seem likely that the levels of butyrate in the circulation or in brain can achieve high enough concentrations to inhibit HDACs in the CNS even after dietary manipulations designed to do so (Stilling et al., 2016).
3. The ability of NaB to block the ghrelin receptor may be the primary mechanism by which it reduces cocaine reward, invoking a role for the gut-brain axis.

For these reasons and others discussed above, it is difficult to conclude that NaB is changing the dependence-like behaviors of drugs of abuse solely by inhibition of HDACs. These drugs of abuse have varying effects of their own on histone acetylation, and in some cases, they increase the levels of histone acetylation much like an HDAC inhibitor (see, for example, Harkness et al., 2013). Additional research on how HDAC inhibitors modify the dependence-like effects of the drugs of abuse should focus on endogenous microbial butyrate production and their interactions with the gut-brain axis.

V. High-Fat Diet

HFDs are most frequently used in combination with drugs of abuse because of the shared neuronal substrates activated by both the DA reward systems in the VTA-NAc axis and in the *substantia nigra*–dorsal striatum axis. These systems are thought to mediate motivation-reinforcement learning and action selection–goal-directed behavior, respectively (Volkow et al., 2017). Many drugs of abuse also interact directly or indirectly with the DA transporter (DAT) to increase the synaptic levels of DA via blocking uptake and/or causing release from presynaptic neurons via reverse transport through the DAT (Baladi et al., 2012a). Compulsive food intake and obesity, such as compulsive drug taking, are significant health problems in the USA. Therefore, a diet rich in fat and sugar could modulate sensitivity to the dependence-like effects of drugs of abuse, most likely by activating the central DA reward systems. HFD-drug interactions generally expose subjects to diets rich in fat and/or sucrose ad libitum or on a restricted access-binge schedule. Thereafter, subjects are tested for dependence-like effects of a drug to determine whether the diet modifies drug-related behavior. Other variables of importance in these studies include sex and subject age (e.g., adolescence, adult, via maternal consumption) at the time of exposure to an experimental diet. In addition to activation of central DA reward pathways, diet and especially an HFD are well known to cause significant alterations in the gut microbiome (Spor et al., 2011; Goodrich et al., 2014; Xiao et al., 2015; Kim et al., 2017; Singh et al., 2017; Ericsson et al., 2018; Hills et al., 2019; Wu et al., 2019; Ezra-Nevo et al., 2020; Wilson et al., 2020), which can in turn alter microbial metabolic profiles that can reverberate throughout the body and into the CNS.

A. High-Fat Diet and Cocaine. Studies investigating the effects of HFD on the actions of cocaine have uncovered a number of interesting complexities, and these publications are highlighted in Table 6. Perhaps the first study to test the effects of an HFD on cocaine was published by Wellman et al. (2007), who reported that acquisition of self-administration was impaired in adult male rats. Morales et al. (2012) found that an HFD decreased the cocaine CPP. These early papers seem to be the exception, however, because most ensuing publications report that an HFD increases cocaine dependence–like behavior. For instance, Puhl et al. (2011) found that a history of restricted or binge-like consumption of an HFD enhances cocaine seeking and self-administration in adult male rats. Exposure of male rats to an HFD-binge intake during adolescence increases the cocaine CPP and self-administration in adulthood (Blanco-Gandía et al., 2017, 2018). These investigators also noted that adolescent rats housed in groups of three to four showed increased sensitivity to the development of a CPP to a subthreshold dose of cocaine, whereas singly housed rats fed standard chow were more sensitive to subthreshold doses of cocaine when tested in adulthood (Blanco-Gandía et al., 2018). To address the question of whether an HFD alters cocaine intake by increasing its rewarding properties or by decreasing its aversive properties, Clasen et al. (2020c) fed an HFD ad libitum to rats from adolescence into adulthood and then tested subjects for development of a CPP and a conditioned place aversion. These investigators reported that long-term exposure to the HFD altered neither the rewarding nor the aversive properties of cocaine (Clasen et al., 2020c). In a follow-up set of experiments, these same investigators reported that ad libitum feeding of an HFD from adolescence into adulthood significantly increased cocaine self-administration (Clasen et al., 2020b). A few studies have exposed pregnant rodents to HFD and then tested the offspring for their responsiveness to cocaine. The results from these studies are not in agreement, with one showing that maternal overnutrition did not alter locomotor responsiveness to cocaine in offspring (Sasaki et al., 2018), whereas a second study found that this treatment resulted in a greater CPP to cocaine in offspring (Peleg-Raibstein et al., 2016). Following the hypothesis that obesity-prone and -resistant rats may have differential sensitivity to natural rewards that could extend to drug

rewards, Thanos et al. (2010) tested obesity-resistant S5B and obesity-prone OM rats for development of a cocaine CPP. These investigators found that obesity-prone OM rats did not show a significant cocaine CPP, whereas the obesity-resistant rats did (Thanos et al., 2010). On the other hand, Townsend et al. (2015) tested obese and lean Zucker rats for cocaine self-administration and found that the two groups did not differ in cocaine intake in a behavioral economic demand procedure. Both groups concluded that the results did not support a theory of common vulnerability for food and nonfood reinforcers despite the overlap in CNS reward pathways mediating each (Thanos et al., 2010; Townsend et al., 2015).

An extensive series of studies by France and colleagues has uncovered numerous interesting results with regard to the influence of sex, age of exposure to a fat-rich diet, and the method of exposure to HFD (restricted vs. ad libitum) on locomotor sensitivity to cocaine. These investigators reported initially that an HFD increased cocaine sensitivity in female rats with both free (Baladi et al., 2012b; Serafine et al., 2015, 2016) and restricted access to the diet (Baladi et al., 2012b). Free but not restricted access to an HFD for adult females also increased sensitivity to cocaine (Baladi et al., 2012b). In another study, Serafine et al. (2014) found that although adult female rats fed an HFD with either free or restricted access showed increased locomotor sensitization to cocaine, the effect of the HFD was not significant. When adolescent female rats were given free access to an HFD paired with either sucrose or saccharin in the drinking water, the development of cocaine locomotor sensitization was enhanced by the diet but not by sucrose or saccharin (Serafine et al., 2015). In contrast with an earlier study (Baladi et al., 2012b), this report found that restricted access to the HFD did not alter the development of locomotor sensitization in adolescent female rats (Serafine et al., 2015). Finally, adult male and female mice given free access to an HFD develop increased sensitization to the locomotor effects of acute cocaine (Collins et al., 2015). With repeated cocaine administration, adult female mice develop locomotor sensitization more rapidly when consuming sucrose, and this effect is not enhanced by an HFD (Collins et al., 2015).

B. High-Fat Diet and Alcohol. A small number of studies have examined the effects of HFD on alcohol drinking, and these studies are highlighted in Table 6. Offspring from dams exposed to an HFD throughout pregnancy and lactation showed increased alcohol drinking in adulthood (Peleg-Raibstein et al., 2016). Adult rats given access to an HFD on an intermittent schedule significantly decreased their alcohol drinking (Sirohi et al., 2017; Villavasso et al., 2019). Coker et al. (2020) carried out an extensive analysis of the impact of HFD access schedules on alcohol drinking, and the results were very interesting. Mice given unlimited access to an HFD showed a significant decrease in drinking, whereas limited access to HFD (3 days/week) did not change alcohol drinking by comparison with controls, and intermittent access (a 24-hour session per week) led to increased alcohol drinking (Coker et al., 2020). It is clear that the discrepancies in the results of these studies may well result from the specific schedule of access to HFD. However, intermittent exposure to an HFD for 6 to 7 weeks can either decrease (Sirohi et al., 2017) or increase (Coker et al., 2020) alcohol drinking, so it appears that additional variables are operational. Data from the studies discussed above supported the conclusion that the observed outcomes were attributed to alterations in neurotransmitter neurochemistry (Peleg-Raibstein et al., 2016; Villavasso et al., 2019), decreased anxiety and elevated ghrelin (Sirohi et al., 2017), and the development of insulin insensitivity and glucose intolerance (Coker et al., 2020).

C. High-Fat Diet and Opiates. Few studies have determined the effects of an HFD on opiate reward, focusing instead on the larger issue of opioid modulation of food intake [see Taha (2010), Bodnar (2019) for reviews]. It has been reported that HFD-induced obesity increases morphine seeking and consumption in rats after bariatric surgery to lower their body weights, but the HFD had no effect on morphine reward in sham controls (Biegler et al., 2016). Rats fed a Western diet (high in palm oil and esterified fats) showed increased morphine reinstatement of an extinguished CPP, whereas rats fed a Mediterranean diet (low in fat) did not show relapse (Milanesi et al., 2019). The latter authors attributed the dietary effects on reinstatement of the morphine CPP to increases in DAT and DA D_2 receptor (DA D_2R) levels in the NAc (Milanesi et al., 2019). These studies are included in Table 6.

D. High-Fat Diet and Methamphetamine, Amphetamine, and Nicotine. The effects of an HFD on methamphetamine, amphetamine, and nicotine reward have scarcely been investigated, and the publications that have done so are highlighted in Table 6. It can be seen that an HFD increases the development of locomotor sensitization to methamphetamine (McGuire et al., 2011). With regard to amphetamine, an HFD decreases drinking (Kanarek et al., 1996) but increases the development of locomotor sensitization in the offspring of dams exposed to an HFD throughout pregnancy and lactation (Peleg-Raibstein et al., 2016). An HFD also decreases the amphetamine CPP (Davis et al., 2008). Mice fed an HFD do not develop a nicotine-induced CPP (Blendy et al., 2005), but after maternal overnutrition, offspring show increased self-administration of nicotine and decreased drug-primed reinstatement (Morganstern et al., 2013). It is clear from these studies that an HFD does not have a unitary effect on the rewarding properties of methamphetamine, amphetamine, or nicotine.

TABLE 6
HFD effects on cocaine, alcohol, methamphetamine, amphetamine, and nicotine reward

Reference	Drug of Abuse	Reward Model	Subjects	Diet	Mode of Exposure and Duration	Outcome	Gut Microbiome Mentioned or Assessed
Wellman et al., (2007)	Cocaine	S/A	Adult ♂ rats	HFD, 35.9% fat	Ad lib, 45 days	↓ ACQ of S/A	No
Puhl et al. (2011)	Cocaine	S/A	Adult ♂ rats	Veg shortening	Ad lib or RES, 6 wk	↑ seeking and S/A	No
Blanco-Gandía et al. (2017)	Cocaine	S/A CPP	Adol ♂ mice → adulthood	HFD 45 kcal % fat	RES, binge, 40 days	↑ CPP to subthreshold dose ↑ S/A	No
Blanco-Gandía et al. (2018)	Cocaine	CPP	Adol ♂ mice	HFD 45 kcal % fat	RES, binge, 40 days	↑ CPP	No
Clasen et al. (2020c)	Cocaine	CPP CTA	Adol ♂ rats → adulthood	HFD 4.5 kcal/g	Ad lib adol → adulthood	CPP formed, not altered by diet CTA formed, not altered by diet	No
Clasen et al. (2020a)	Cocaine	S/A	Adol ♂ rats → adulthood	HFD 4.5 kcal/g	Ad lib adol → adulthood	↑ S/A	No
Baladi et al. (2012b)	Cocaine	LS	Adol ♀ rats, adult ♀ rats	HFD 34.3% fat	Ad lib 1 or 4 wk, RES 1 or 4 wk	↑ LS after 1 wk HFD in adol and adult rats ↑ LS after 4 wk HFD for RES but not ad lib	No
Morales et al. (2012)	Cocaine	CPP	Adol ♂ mice	HFD 45 kcal % fat	Ad lib 28 days	↓ CPP	No
Serafine et al. (2014)	Cocaine	LS	Adult ♀ rats	HFD 34.3% fat	Ad lib and RES	↑ LA but HFD did not alter ad lib or RES exposure	No
Serafine et al. (2015)	Cocaine	LS	Adol ♀ rats	HFD 60 kcal % fat	Ad lib and RES	↑ LS under ad lib; no change under RES	No
Baladi et al. (2015)	Cocaine	LS	Adol ♂ rats, adult ♂ rats	HFD 34.3% fat	Ad lib and RES	Adol HFD ↑ LS under ad lib and RES access; Adult no Δ in LS under ad lib and RES access	No
Serafine et al. (2016)	Cocaine	LS	Adol ♀ rats	HFD 34.4% fat	Ad lib 35 days	↑ LS	No
Collins et al. (2015)	Cocaine	LS	Adult ♀and ♂ mice	HFD 34.3% fat	Ad lib up to 12 wk	↑ LS to acute cocaine in ♂ and ♀, ↑ LS faster to repeated cocaine in ♀ drinking sucrose	No
Peleg-Raibstein et al. (2016)	Cocaine	CPP	Adult ♀and ♂ mice	Maternal HFD 60% energy from fat	Ad lib 9 wk	Maternal HFD ↑ CPP in offspring	No
Sasaki et al. (2018)	Cocaine	LS	Adult ♀ and ♂ rats	Maternal HFD 5.24 kcal % fat	Ad lib 4 wk before mating and through	Maternal HFD no effect on COC LS in offspring	No
Thanos et al. (2010)	Cocaine	CPP	Adult ♂ OM and S5B rats	STD diet	Ad lib	OM rats show no CPP; S5B rats develop CPP	No
Townsend et al. (2015)	Cocaine	S/A	Adult ♂ Zucker obese and lean rats	STD diet	Ad lib	Obese and lean rats show no change in demand for S/A	No
Peleg-Raibstein et al. (2016)	Alcohol	S/A	Adult ♀and ♂ mice	Maternal HFD 60% energy from fat	Ad lib 9 wk	Maternal HFD ↑ S/A in offspring	No
Sirohi et al. (2017)	Alcohol	S/A	Adult ♂ rats	HFD 4.41 kcal % fat	RES 6 wk	↓ AD	No
Villavasso et al. (2019)	Alcohol	S/A	Adult ♂ rats	HFD 40% kcal fat	RES 1 or 2 wk	↓ AD	No
Coker et al. (2020)	Alcohol	S/A	Adult ♂ mice	HFD 60% fat calories	Ad lib 6 to 7 wk, unlimited 6 to 7 wk, RES 6 to 7 wk	↓ AD; no Δ from control chow ↑ alcohol drinking	No
Biegler et al. (2016)	Morphine	S/A	Adult rats	HFD 60% kcal fat	Ad lib 26–28 wk	No effect on consumption or seeking in sham controls for bariatric surgery	No
Milanesi et al. (2019)	Morphine	CPP	Adult ♂ rats	Western (20% ↑ fat) vs. Mediterranean	Ad lib 10 wk	↑ CPP REL	No
Kanarek et al. (1996)	Amphetamine	S/A	Adult ♂ rats	Hydrogenated vegetable fat 9 kcal/g	Ad lib 4 wk	↓ drug drinking	No
Davis et al. (2008)	Amphetamine	CPP	Adult ♂ rats	HFD 1.71 kcal/g from fat	Ad lib 12 wk	↓ CPP	No
Peleg-Raibstein et al. (2016)	Amphetamine	LS	Adult ♀and ♂ mice	Maternal HFD 60% energy from fat	Ad lib 9 wk	Maternal HFD ↑ LS in offspring	No
Blendy et al. (2005)	Nicotine	CPP	Adult ♂ mice	HFD 45 kcal% fat	Ad lib 15 wk	No development of CPP	No
Morganstern et al. (2013)	Nicotine	S/A	Adult ♂ rats	Maternal HFD 60% 5.2 kcal/g fat	Ad lib during gestation	↑ S/A and ↓ REL	No

↓, decreases; ↑, increases; →, continuing to; ♀, female; ♂, male; Δ, change; ACQ, acquisition; AD, alcohol drinking; adol, adolescent; COC, cocaine; CTA, conditioned taste aversion; LA, locomotor activity; LS, locomotor sensitization; OM, Osborne-Mendel obesity-prone rat; RES, restricted access; S/A, self-administration; S5B, obesity-resistant rat; STD, standard diet; veg, vegetable.

Most investigators attribute dietary effects on the rewarding properties of these drugs to overlapping reward pathways shared by overeating and drugs of abuse or to the anorectic effects of the amphetamines.

E. Summary and Alternative Interpretations of Studies Examining Effects of High-Fat Diet on the Rewarding Effects of Drugs of Abuse. Interpretation of the results of studies examining how an HFD changes sensitivity to cocaine within the construct of activation of overlapping DA reward pathways by fat and cocaine is complex. In general, it appears that an HFD increases sensitivity to the cocaine reward, but the results must be tempered because of some variability in outcomes. Interpretation is made more complex by the roles played by sex, age of subject when exposed to an HFD, the duration of exposure to the HFD, and animal housing conditions. Studies using self-administration and CPP agree that longer-term exposure of adolescent or adult male rodents to an HFD increases cocaine self-administration and development of a CPP. The fact that exposure to an HFD in adolescence, a time of enhanced vulnerability, extends heightened sensitivity to cocaine into adulthood is interesting and significant. Results from studies using obese versus lean animals fed standard diets and those that used cocaine-induced locomotor sensitization as the behavioral model show less agreement. Some of the more perplexing outcomes relate to the observation that an HFD enhances the locomotor-stimulating effects of cocaine in adolescent male rats but, against predictions, decreases striatal DA clearance, which led Baladi et al. (2015) to rule out the DAT as a mediator of the observed effects. Fish oil, which was used because of its documented ability to counter the inflammatory effects of HFDs, was found to prevent HFD-induced enhancement of locomotor sensitivity of adolescent females to cocaine, but its effects could not be linked to reductions in inflammatory cytokine markers (Serafine et al., 2016). The differential sensitivity of males and females to the locomotor-sensitizing effects of cocaine is also difficult to reconcile within the construct of the DA reward system (see Baladi et al., 2012a for review). Lastly, the finding that obesity-prone OM rats did not develop a cocaine CPP ran counter to expectations (Thanos et al., 2010). In this same study, the ability of the DA D_2R antagonist bromocriptine to reduce the cocaine CPP in obesity-resistant S5B rats led the authors to conclude that the DA D_2R played a partial regulatory role in the resistant rats. However, this effect was confounded somewhat by the observation that bromocriptine significantly reduced time spent in the cocaine-paired chamber in the obesity-prone OM rats even though these subjects did not form a cocaine CPP (Thanos et al., 2010). For more extended discussions of how diet, food bingeing, and the DA reward system can interact to alter the rewarding properties of various drugs of abuse, the interested reader is referred to the following selected reviews: Bello and Hajnal (2010), Baladi et al. (2012a), Billing and Ersche (2015), de Macedo et al. (2016), Blanco-Gandía and Rodríguez-Arias (2017), and Volkow et al. (2017).

None of the publications discussed above include consideration of the gut microbiome in the interpretation of the results on drug-HFD interactions. However, it is clear that many of the variables that influence how an HFD can modulate the rewarding effects of drugs of abuse are closely linked to the gut microbiome, and for the reasons listed below, the gut microbiome cannot be ruled out:

1. An HFD causes extensive alterations in the composition and structure of the gut microbiome, so animals fed an HFD are metabolically quite different from animals fed standard laboratory chow. The administration of cocaine, alcohol, or amphetamines (which also alter the gut microbiome composition) on these differing backgrounds could have effects that are influenced as much by the dysbiotic microbiome as by alterations of central DA reward pathways.
2. Different housing conditions influence how an HFD modulates cocaine sensitization, but grouped versus individual housing has a significant impact on the gut microbiome as well (Spor et al., 2011; Xiao et al., 2015; Ericsson et al., 2018; Hylander and Repasky, 2019; Ringel-Scaia et al., 2019; Robertson et al., 2019).
3. Male-female differences influence the development of cocaine-induced locomotor sensitization, and they exert strong influence on the gut microbiome (Gomez *et al.*, 2012; Markle *et al.*, 2013; Xiao *et al.*, 2015; Jašarević *et al.*, 2016; Davis *et al.*, 2017; Beale *et al.*, 2019). Of particular relevance is the finding that high-fat and high-sucrose diets differentially affect the gut microbiome of males and females (Daly et al., 2020).
4. Maternal obesity may influence cocaine reward in offspring, but it certainly exerts a powerful influence on the gut microbiome of offspring that persists into young adulthood (Buffington et al., 2016; Guo et al., 2018; Zhou and Xiao, 2018).
5. The differing responses of at least the lean and obese Zucker rats to cocaine could be influenced by the vastly differing gut microbiomes in these rats (Hakkak et al., 2017).

VI. Summary, Conclusions, and Perspectives

Over the past 10–15 years, a large number of studies have investigated the effects of antibiotics, NaB, and an HFD on the rewarding effects of many drugs of abuse, and the greatest amount of focus has been on cocaine and alcohol. β-Lactam antibiotics were used in these studies for their ability to increase the levels of the GLT1 in the NAc. It now turns out that there is no

relationship between the levels of expression of the GLT1 after treatment with β-lactam antibiotics and alterations in drug reward. In addition, the results of these studies also reveal significant variability with drug reward being increased, decreased, or not changed by antibiotics. Some of the variations seen in the highlighted studies can be linked directly to alterations in the gut microbiome. First, most drugs of abuse are now known to cause significant alterations in the composition of the gut microbiome. Second, all antibiotics used to alter drug reward are known to cause significant changes in the gut microbial communities as well. Third, any pairing of a particular drug of abuse (e.g., cocaine) with a particular antibiotic (e.g., CTX) will alter the gut microbiome in a manner that is specific for each drug in the pairing (see Ianiro et al., 2016 for examples of antibiotic specificity). Despite the overwhelmingly clear effects of antibiotics on the gut microbiome, all studies so far have focused on central mechanisms by which antibiotics alter the rewarding effects of drugs of abuse (e.g., mGluR2/3 vs. GLT1 Logan et al., 2020). In the absence of a relationship between the levels of GLT1 and alterations in drug reward by antibiotics, the knockdown of the gut microbiome by antibiotics remains an obvious, potential mechanism by which drug reward is altered, but unfortunately, the gut microbiome has not entered into the conceptualization of how antibiotics alter drug reward. Many of the highlighted studies even use the term "β-lactam antibiotic" in the title of published papers without any consideration that the effects of these antibiotics on drug reward could be occurring outside of the CNS.

A number of studies used NaB to alter drug reward, focusing on the ability of this compound to inhibit histone deacetylase enzymes. The outcomes of these studies are similar to those using antibiotics in that high doses of NaB can increase, decrease, or have no effect on drug reward. NaB is a short-chain fatty acid and a fermentation product of the gut microbiome that can also alter the structure and composition of the gut microbiome when given exogenously. Despite being given in very large doses (e.g., 1200 mg/kg), NaB is a weak inhibitor of HDACs because of the limited bioavailability it achieves in vivo. In vitro studies have established that NaB is a broad-spectrum HDAC inhibitor that exerts actions on class I (HDACs 1, 2, 3, and 8) and class IIa (HDACs 4, 5, 7, and 9) HDACs, so it is difficult to link drug actions to any specific enzyme form. It is likely the case that drug reward is mediated in part by epigenetic alterations (Nestler, 2014; Cadet, 2016; Ajonijebu et al., 2017), but it should be remembered that NaB and other SCFAs can cause epigenetic changes in the gut microbiome as well, and communication between the microbiome and host is mediated in part via epigenetic mechanisms (for reviews see Hullar and Fu, 2014; Alam et al., 2017; Aleksandrova et al., 2017; McKenzie et al., 2017; Kim and Jazwinski, 2018). Finally, the ability of NaB and other SCFAs to influence drug reward by interfering with ghrelin signaling represents another influential, peripherally based mechanism.

Feeding animals an HFD has generally been undertaken to study how overlapping food and drug reward mechanisms interact to modify drug reward. HFDs have varying effects on drug reward and can increase, decrease, or have little influence depending on the drug, the fat content of the diet, and the duration of the nutritional modification. Alcohol is unique among drugs of abuse in that it is nutritive and its interactions with CNS reward circuits and the gut microbiome differ from those of non-nutritive drugs of abuse (Alhadeff et al., 2019). On the other hand, diet is one of the most important determinants of the structure and composition of the gut microbiome. Both overnutrition (Spor et al., 2011; Goodrich et al., 2014; Xiao et al., 2015; Singh et al., 2017; Kim et al., 2017; Ericsson et al., 2018; Hills et al., 2019; Wu et al., 2019; Ezra-Nevo et al., 2020; Wilson et al., 2020) and undernutrition (Sonnenburg and Sonnenburg, 2014; Sonnenburg et al., 2016) cause extensive alterations in the gut microbiome. As is the case with studies of antibiotics and drugs of abuse, the combination of drug-induced dysbiosis with dietary-induced dysbiosis will have effects on the gut microbiome that are specific to each pairing of a drug of abuse with an altered diet and that are different from either treatment alone. Adding to this complexity is the fact that selected drugs of abuse have GI effects (e.g., opiate constipation, cocaine ischemia) that can influence the gut microbiome in a manner that is different from drugs of abuse that do not have deleterious effects on GI function. With the foregoing discussion in mind, it is plausible to conclude that a role for the gut microbiome in SUDs cannot be ruled out and should be given additional attention going forward.

A large number of factors are thought to contribute to the variation in outcomes of studies of drugs of abuse and how antibiotics, NaB, and HFDs interact to modify their rewarding properties. These include sex, prenatal exposure to drugs and modifiers, ad libitum versus binge feeding of altered diets, and the age of experimental subjects, to list a few. As more is learned about how the gut microbiome influences host health and well-being, it has become clear that these variables can have significant effects on the composition of the gut microbiome. In turn, these variables can contribute to the variability and irreproducibility seen in many animal models of disease (Franklin and Ericsson, 2017). Factors that may seem trivial are now known to disrupt the gut microbiome in rodents. Xiao et al. (2015) investigated some of those factors that have broad effects on the design and outcomes of experiments with mice and observed five major ones: mouse provider, housing laboratory/room, diet, sex, and mouse strain. The impact of these factors has been affirmed in other

studies (Spor et al., 2011; Goodrich et al., 2014; Franklin and Ericsson, 2017; Ericsson et al., 2018). For example, regarding mouse vendors, C57BL/6 mice from Jackson Laboratory or Taconic Farms have significantly distinct microbiomes (Robertson et al., 2019). Other influential factors include drinking water, the birth/nursing dam, type of caging (e.g., static, ventilated), bedding, housing (e.g., single, grouped), fasting, and the maternal/cage effect (Spor et al., 2011; Goodrich et al., 2014; Franklin and Ericsson, 2017; Kim et al., 2017; Ericsson et al., 2018). With these factors in mind, it is easy to imagine that any one of them or several in combination can introduce unanticipated influences into an experiment, particularly when considering that drugs of abuse alter the gut microbiome.

Many other mechanisms exist by which the gut microbiome could modify the rewarding actions of drugs of abuse. A complete discussion of these mechanisms is well beyond the scope of this review, but a few examples are highly relevant and deserve mention. First, a very large number of marketed, nonantibiotic drugs are now known to have extensive impact on gut bacteria, and CNS-active drugs are overrepresented among all tested drugs for their ability to inhibit growth of selected bacterial strains (Maier et al., 2018). With few accepted medical uses, drugs of abuse have not been tested extensively for their bacteriostatic or bactericidal effects, but it is known that at least cocaine possesses significant antimicrobial activity (Johnson et al., 2008). Second, the gut microbiome has both direct and indirect effects on drug and xenobiotic metabolism (Wilson and Nicholson, 2017; Clarke et al., 2019; Zimmermann et al., 2019). For instance, the gut microbiome can carry out reductive metabolism and other biotransformations, including demethylation, deamination, dihydroxylation, decarboxylation, and oxidation (Wilson and Nicholson, 2017). Demethylation of methamphetamine by intestinal bacteria (Caldwell and Hawksworth, 1973) is but one example of how the metabolism, disposition, and bioavailability of a drug of abuse can be determined by gut bacteria. Third, alterations in tryptophan metabolism by the gut microbiome can modify the downstream kynurenine pathway (Kennedy et al., 2017), and it has been demonstrated that increases in kynurenic acid significantly reduce cue-induced reinstatement of both alcohol and cocaine-seeking behavior (Vengeliene et al., 2016). Increases in brain kynurenine levels also reduce alcohol consumption via its ability to inhibit DA release in the NAc (Giménez-Gómez et al., 2018). Fourth, and as mentioned above in paragraph IV, increases in butyrate production by the gut microbiome could interfere with ghrelin signaling, which is known to have profound effects on the rewarding effects of alcohol, stimulants, and nicotine (see Panagopoulos and Ralevski, 2014 and Zallar et al., 2017 for reviews). Last, the gut microbiome produces a large number of metabolites that agonize numerous G-protein–coupled receptors (Cohen et al., 2017; Park et al., 2019), including various receptor subtypes for serotonin and DA (Chen et al., 2019; Colosimo et al., 2019). Therefore, alterations in gut production of these metabolites could interact with the same receptors implicated in the rewarding effects of drugs of abuse, such as the mGluR2 for reinstatement of cocaine seeking after treatment with CTX (Logan et al., 2020).

Based on the studies highlighted in Tables 1–6, it is clear that the gut microbiome has received very little attention in the interpretation of results from studies testing antibiotic, NaB, or HFD interactions with drugs of abuse. However, it is undeniable that β-lactam antibiotics and HFDs cause substantial disruptions of the gut microbiome. Drug-induced dysbiosis could also shift the makeup of the microbiome such that experimental animals differ from controls not only based on drug treatment but on the interaction of that particular drug with numerous other dysbiosis-causing factors. More direct and specific assessment of the role of the gut microbiome in SUDs could lead to a better understanding of the mechanisms underlying drug abuse and thereby suggest new therapies. Although it is still too early to consider them for the treatment of SUD-related complications, manipulations of the gut microbiome–brain axis through supplementation of nutritional dietary components, such as prebiotics (i.e., indigestible fiber), and probiotics (beneficial live microorganisms) (Liu et al., 2015), as well as fecal microbiota transplantation constitute available tools that could aid in the design of studies aiming to assess the potential role of the gut microbiome in SUDs. Accounting for the potential roles played by the gut microbiome in SUDs, especially when using animal models, would increase experimental rigor and reproducibility and reduce variability in outcomes.

Authorship Contributions

Participated in research design: Angoa-Pérez, Kuhn.

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