Title
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Journal
Behavioural Pharmacology, 31(2&3)

ISSN
0955-8810

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Publication Date
2020-04-01

DOI
10.1097/fbp.0000000000000538

Peer reviewed

HHS Public Access

Author manuscript

Behav Pharmacol. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Behav Pharmacol. 2020 April ; 31(2-#x000263): 113–121. doi:10.1097/FBP.0000000000000538.

The Role of the Gut Microbiome in Opioid Use

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Abstract

Although the gut and brain are separate organs, they communicate with each other via trillions of intestinal bacteria that collectively make up one's gut microbiome. Findings from both humans and animals support a critical role of gut microbes in regulating brain function, mood, and behavior. Gut bacteria influence neural circuits that are notably affected in addiction-related behaviors. These include circuits involved in stress, reward, and motivation, with substance use influencing gut microbial abnormalities, suggesting significant gut-brain interactions in drug addiction. Given the overwhelming rates of opioid overdose deaths driven by abuse and addiction, it is essential to characterize mechanisms mediating the abuse potential of opioids. We discuss in this review the role of gut microbiota in factors that influence opioid addiction, including incentive salience, reward, tolerance, withdrawal, stress, and compromised executive function. We present clinical and preclinical evidence supporting a bidirectional relationship between gut microbiota and opioid-related behaviors by highlighting the effects of opioid use on gut bacteria, and the effects of gut bacteria on behavioral responses to opioids. Further, we discuss possible mechanisms of this gut-brain communication influencing opioid use. By clarifying the relationship between the gut microbiome and opioid-related behaviors, we improve understanding on mechanisms mediating reward-, motivation-, and stress-related behaviors and disorders, which may contribute to the development of effective, targeted therapeutic interventions in opioid dependence and addiction.

Keywords

Gut-Brain Axis; Motivation; Bacteria; Dopamine; Stress; Reward; Mood; Addiction

Introduction

A growing field in human health is the gut-brain connection, a notion that our gut health is directly related to our emotional health. Although the gut and brain are separate organs, they are connected physically via the vagus nerve, and biochemically via neurotransmitters, gut

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Conflicts of Interest: None

hormones, microbial metabolites, and the immune system (Dinan and Cryan, 2012). Bidirectional communication between the central nervous system (brain) and enteric nervous system (gut) occurs through the gut-brain axis, which is maintained by the trillions of intestinal bacteria that collectively make up one's gut microbiome.

An abundance of evidence in both humans and animals supports an essential role of gut microbiota in regulating brain function, mood, stress, and behavioral responses to rewards, including food and drugs of abuse (Collins and Bercik, 2009; Diaz Heijtz et al., 2011; Clarke et al., 2013; Selkrig et al., 2014; Cussotto et al., 2018). Gut bacteria are heavily impacted by "diseased" states, as abnormalities in gut microbial communities, or dysbiosis, are observed in patients diagnosed with substance use disorder, depression, anxiety, Parkinson's disease, autism, and/or schizophrenia (Schroeder and Bäckhed, 2016). Disruption to a hos's normal microbiota can lead to exaggerated stress responses and depressive symptoms (Sudo et al., 2004; Ait-Belgnaoui et al., 2014; Tarr et al., 2015; Kelly et al., 2016; Leclercq et al. 2016; Rea et al., 2016), further supporting the bidirectional relationship between the gut and brain. Given the significance of gut bacteria in obesity, stress, and motivated behaviors, as well as the extensive overlap in neuroadaptations between overeating and drug abuse (Volkow et al., 2017) and the key roles of stress and reward processing in the development of addiction, we review available literature to support the hypothesis that gut-brain communication is necessary in the development and perpetuation of drug addiction.

Addiction is a chronic brain disorder that alters circuitry involved in reward, stress, learning, memory, and motivation. The development of drug addiction is driven by exaggerated incentive salience, reward deficits, stress surfeits, and compromised executive function in three distinct stages, namely binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving) (Koob and Volkow, 2016). Opioid addiction is the leading cause of drug overdose in the United States and is characterized by a compulsion to seek and voluntarily take opioids owing to their reinforcing effects and an impaired ability to control intake despite physical or psychological harm (Scholl et al., 2018). Due to the rapid increase in numbers of opioid-related disabilities and deaths throughout the world (Martins et al., 2015), this review is focused on gut-brain interactions specifically in opioid use.

The endogenous opioid system regulates pain relief, reward processing, emotion, stress, and autonomic control, and consists of mu, delta, and kappa receptors (Benarroch, 2012). Opioid receptors are distributed widely throughout the brain, periphery, and gut (De Schepper et al., 2004), and are activated endogenously by enkephalins, dynorphins, endorphins, and endomorphins, as well as exogenously by opioids (e.g., heroin, morphine, oxycodone, fentanyl). Opioids exert their primary clinical effects on mu opioid receptors to reduce pain perception. A link between gut health and opioid intake is evident in the ability of opioids to significantly impact gastrointestinal function (i.e. opioid-induced constipation). Indeed, opioid use is associated with gut dysbiosis in both humans (Vincent et al., 2016; Wang and Roy, 2016; Zhernakova et al., 2016; Acharya et al., 2017; Xu et al., 2017; Barengolts et al., 2018) and animals (Meng et al., 2013; Meng et al., 2015; Banerjee et al., 2016; Kang et al., 2017; Lee et al., 2018; Wang et al., 2018). Preclinical studies have also shown an important role of the gut microbiome in drug reward (Kiraly et al., 2016; Lee et al., 2018) and the development of opioid tolerance (Kang et al., 2017). In this review, we present available

literature assessing the bidirectional role of the gut-brain axis in addiction- and opioid-related behaviors, including stress, reward, incentive salience, mood disruption, tolerance, dependence, withdrawal, and antinociception, as well as propose possible mechanisms of gut-brain interactions in opioid use.

With the prevailing opioid crisis and escalating numbers of opioid-related deaths worldwide driven by addiction, it is critical to evaluate mechanisms that mediate the abuse potential of opioids. By presenting a specific role of the gut-brain axis in opioid use and in factors that influence addiction, we provide a potential therapeutic target integrated with opioid regimens to mitigate abuse and addiction vulnerability. Novel interventions to limit the negative clinical outcomes of opioid use, such as tolerance, dependence, and withdrawal, may reduce the risk of addiction and opioid-related deaths. An improved understanding of how the gut is involved in addiction-related behaviors can also contribute to the development of effective treatment strategies in other disorders with shared characteristics, including depression, anxiety, and chronic pain.

Methods to study the gut microbiome

While human subjects provide valuable translational data, the majority of our understanding of gut-brain interactions in addiction-related behaviors comes from preclinical rodent studies. Animal models allow specific, targeted manipulation of gut microbiota while controlling for factors that are widely variable in humans, including disease comorbidities, opioid dose and duration of use, co-use of other opioid and/or non-opioid drugs, drug history, and genetics. Comparing human microbiomes of substance use disorder versus healthy controls may also reflect differences in lifestyles and diets and are therefore difficult to appoint solely to drug use.

The four primary ways that gut microbiota can be manipulated are with probiotics, prebiotics, antibiotics, and fecal microbiota transplantation (FMT). Probiotics are live, beneficial bacterial strains that do not repopulate on their own so need to be administered daily for benefits to the host. Prebiotics are dietary fibers that are indigestible by the host and undergo bacterial fermentation to stimulate the growth of certain types of bacteria. An alternative to prebiotics is administration of short-chain fatty acids (SCFAs), which are bacterial fermentation byproducts. Depletion of 70-90 percent of gut bacteria in rodents can be achieved with prolonged oral treatment of non-absorbable antibiotics that do not mirror clinical doses (Bercik et al., 2011; Reikvam et al., 2011). The goal of FMT, often known as stool transplantation, fecal transplantation, or fecal bacteriotherapy, is to restore eubiosis by transferring stool from a healthy donor into a recipient with an altered colonic microbiome (Vindigni and Surawicz, 2017). FMT is an effective treatment for recurrent *Clostridium difficile* infection that has not responded to standard therapy. Potential applications of FMT for intervention in non-gastrointestinal diseases, such as obesity, ischemic stroke, Parkinson's disease, Alzheimer's disease, and depression, are also being explored (Kelly et al., 2016; Sampson et al., 2016; Chen et al., 2019; Dutta et al., 2019; Muscogiuri et al., 2019; Sun et al., 2019).

A unique animal model used in microbiome research is the germ-free mouse, in which mice are raised in a sterile environment from birth and remain completely absent of internal or external microbes (Faith et al., 2010). Germ-free mice are usually compared with mice containing known pathogens (conventional or specific pathogen-free) and can be colonized with microbial communities from donor animals or human subjects. Although the germ-free animal model is not entirely clinically relevant, as humans have constant exposure to environmental microbes immediately after birth, its use provides insight into early host development and function. Gut microbial depletion via prolonged oral antibiotic administration bypasses the perinatal developmental period.

As the bulk of intestinal bacteria are excreted in fecal matter, microbial analysis is most commonly achieved from fecal samples. Gut bacterial profiles are analyzed by DNA sequencing of the 16S rRNA gene found in all bacteria. Specific primers can select for the variable regions of the 16S gene to provide a profile of the different bacterial species in a given sample. DNA sequencing of bacterial genes reveals a sample's bacterial abundance, alpha diversity (i.e. how many different species exist in the sample), and beta diversity (i.e. different species in one sample compared to another sample).

Gut microbiome role in incentive salience

Addiction is a chronic brain disease that is associated with dysregulation of reward and motivation. Incentive salience is a motivational property that when attributed to reward-predicting stimuli, or cues, triggers the approach toward and consumption of a reward (Tindell et al., 2009; Zhang et al., 2009). The development of incentive salience is mediated by the mesolimbic dopamine system and promotes habits that encourage excessive cue-induced drug seeking and self-administration behaviors (Berridge 2012).

A vagal gut-to-brain circuit has been established to play a critical role in reward and motivation (Han et al., 2018), and gut bacteria influence how animals respond to various rewards, such as food and drugs (Korner and Leibel, 2003; Duca et al., 2012; Alcock et al., 2014; Kiraly et al., 2016; de Wouw et al., 2018; Lee et al., 2018; Al-Ghezi et al., 2019). Natural rewards, such as food, sex, and nurturing, are processed by key mesocorticolimbic structures and neurotransmitters, including the ventral tegmental area (VTA), nucleus accumbens, prefrontal cortex, dopamine, serotonin, GABA, glutamate, and endogenous opioids (Russo and Nestler, 2013). Drugs of abuse, including opioids, alcohol, stimulants, and cannabis, are artificial rewards that hijack this same brain system, and repeated drug use induces neurophysiological changes that contribute to addiction (Volkow and Morales, 2015).

Passive exposure to or voluntary consumption of drugs of abuse can induce imbalances in gut microbiota in humans and rodents (Volpe et al., 2014; Wang and Roy, 2016; Ning et al., 2017; Temko et al., 2017; Hillemacher et al., 2018; Hofford et al., 2018). In line with bidirectional gut-brain communication, these microbial imbalances influence brain function and behavior. Gut dysbiosis is associated with decreased levels of serotonin and dopamine, both important reward-related neurotransmitters (Yano et al., 2015), and changes in the gut microbiome are correlated with altered striatal dopamine receptor expression in a model of

compulsive alcohol seeking (Jadhav et al., 2018). Additionally, mice with depleted gut microbiota have abnormal behavioral responses to cocaine reward compared to controls (Kiraly et al., 2016; Lee et al., 2018), further highlighting a feedback loop between impaired reward processing and gut dysbiosis.

A growing amount of work has investigated the role of gut bacteria in obesity and overeating, which is relatable to drug addiction, as clinical and preclinical evidence uncover a significant overlap of neuroadaptations in overeating (food addiction) and drug addiction (Volkow et al., 2017). The rewarding properties of food and drugs are necessary for addictive potential, as foods that are highly palatable or drugs that produce significant euphoria promote repeated consumption or intake. Further, the rewarding properties of food or drugs are necessary for attributing positive motivational value to stimuli associated with reward availability and act as powerful incentives of rewardseeking behavior (Di Chiara, 1999). Consistent with food and drug reward sharing similar neural mechanisms, current pharmacological and non-pharmacological (i.e. vagal nerve stimulation) treatments for obesity have also shown efficacy in reducing self-administration and/or rewarding effects of alcohol, cocaine, opiates, and nicotine in rodents (Egecioglu et al., 2013; Graham et al., 2013; Skibicka, 2013; Engel and Jerlhag, 2014; Schmidt et al., 2016; Sirohi et al., 2016; Vallof et al., 2016; Childs et al., 2017; Fortin and Roitman, 2017; Tuesta et al., 2017).

As expected, the reward system is more stimulated by high energy-dense food than low-calorie food (van der Laan et al., 2014). High-fat or high-sucrose diets are associated with altered microbial diversity in mice (Daniel et al., 2014; B. Liu et al., 2018; Magnusson et al., 2015), and these diet-induced microbial changes substantially influence brain function, resulting in reduced synaptic plasticity, increased vulnerability to anxiety-like behavior, impairment in long-term and short-term memory, and disruptions in exploratory behavior (Sharma et al., 2012; Bruce-Keller et al., 2015). Bacterial byproducts that come into contact with gut epithelium stimulate production of gut hormones and neuropeptides, including peptide YY, cholecystokinin, glucagon-like peptide-1, and substance P, which mediate hunger and satiety signaling (Cani et al., 2013; Cani and Knauf, 2016). These findings highlight a critical function of gut bacteria in regulating appetite and feeding behaviors.

Although similar neural pathways influence food and drug reward, bariatric surgery (e.g. gastric bypass) to effectively reduce food intake, increases vulnerability and sensitivity to the reinforcing effects of opioid analgesics (Raebel et al., 2013; Biegler et al., 2016). This may be explained by the transference of one addiction (food) to another, as surgery eliminates excessive eating but does not alter individual predispositions to addictive behaviors (Niego et al., 2007; Pepino et al., 2014). In addition, altered gastrointestinal anatomy may cause changes in pharmacokinetics, as opioids are absorbed in the gastrointestinal tract (Tan et al., 1989; Lotsch et al., 1999).

Gut microbiome role in drug withdrawal/negative affect

Various biological factors likely contribute to increasing chronic opioid use, including higher pain sensitivity and lower pain detection thresholds (Dodet et al., 2013). The shift from acute drug use to addiction may be due to opposing brain circuits that mediate stress and reward,

as addiction progresses from initial drug use for reward (i.e. positive reinforcement) to repeated use for distress avoidance (i.e. negative reinforcement). Once an individual adapts to regular use of opioids, a sudden decrease in intake leads to withdrawal, which interestingly yields symptoms opposite of opioid effects, as the brain tries to compensate against homeostatic disruption. The withdrawal/negative affect stage of the addiction cycle is represented by dampened reward via dopamine deficits and increased stress via activation of corticotropin-releasing factor and dynorphin (Koob et al., 2014). This recruitment of the stress system results in an emergence of negative emotional states, including dysphoria, anxiety, irritability, and depression. Baseline stress levels are heightened and exacerbated during withdrawal or extended abstinence, which encourages a cycle of continual drug intake to avoid the dysphoric feelings associated with the negative affect.

Stress, both acute and chronic, plays a key role in mediating an animal's sensitivity to food and drug reinforcers (Sinha and Jastreboff, 2013; Yau and Potenza, 2013; Koob et al., 2014) and is a primary risk factor in the development of drug abuse and addiction. A substantial amount of evidence supports a bidirectional and causal relationship between gut dysbiosis and stress. Gut microbiota directly modulate general stress responses as well as drug withdrawal-induced anxiety (Xiao et al., 2018). Imbalances in gut microbial communities lead to a heightened activation of the hypothalamic-pituitary-adrenal (HPA) axis stress response (Sudo Nobuyuki et al., 2004; Ait-Belgnaoui et al., 2014; Tarr et al., 2015; Gacias et al., 2016; Leclercq et al., 2016; Rea et al., 2016), and restoring eubiosis via probiotics, SCFAs, and FMT ameliorates stress-related biomarkers and behaviors (Desbonnet et al., 2010; Ait-Belgnaoui et al., 2012; Liang et al., 2013; Pusceddu et al., 2015; Schmidt et al., 2015; Tarr et al., 2015). In addition, stress induces changes in microbiota composition and intestinal barrier function (Söderholm et al., 2002; Gareau et al., 2008). This is perhaps unsurprising given the considerable impact that stress has in aggravating gastrointestinal disorders and symptoms, such as inflammatory bowel disease, irritable bowel syndrome, gastric ulcers, and diarrhea (Klooker et al., 2009; Mayer, 2011; Moloney et al., 2016).

Substance use disorders are also highly comorbid with depression and anxiety, which are both characterized as stress-related mood disorders, in which stress is a major risk factor in its onset, and affected individuals have increased stress sensitivity (Holsboer, 2000; Kendler et al., 2006; Scott et al., 2013; Yang et al., 2015; Ramirez et al., 2016). Impaired gut microbiota is reported in depression (Desbonnet et al., 2010; Jiang et al., 2015; Kelly et al., 2016; Luna and Foster, 2015; Macedo et al., 2017) and anxiety (Neufeld et al., 2011; Luna and Foster, 2015; Tarr et al., 2015), as well as other central nervous system abnormalities and diseases, such as hyperactivity, cognitive deficits, Parkinson's disease, and schizophrenia (Diaz Heijtz et al., 2011; Schepeijans et al., 2015; Frohlich et al., 2016; Severance and Yolken, 2018). This link between central nervous system disorders and dysbiosis is not simply an association, as transplantation of gut bacteria from humans or animal models with obesity, chronic pain, anxiety, depression, Parkinson's disease, or schizophrenia produces matching abnormal behaviors in animals (Bravo et al., 2011; Bruce-Keller et al., 2015; Kelly et al., 2016; C. Yang et al., 2019; Zhu et al., 2019). Further, gut bacterial depletion in mice increases depressive-like behavior, alters visceral pain responses, and impairs cognition (O'Mahony et al., 2015; Fröhlich et al., 2016). Similarly in humans, a single treatment course of antibiotics is associated with an increased risk of depression and

anxiety that rises with recurrent antibiotic exposure (Lurie et al., 2015). These findings collectively suggest a feedback loop exists between stress, depressive states, and gut dysbiosis, which could underlie the gut microbiome's role in drug withdrawal/negative affect.

Gut microbiome role in drug anticipation/craving

The preoccupation/anticipation stage is often linked with drug craving and hypothesized to be a key element in relapse. During this stage, the combination of excessive drug cue-induced incentive salience, diminished reward system function, and heightened stress levels promotes pathological drug seeking. Motivational withdrawal syndrome develops when access to a drug is prevented, where the primary focus is to alleviate withdrawal symptoms. According to Pavlovian conditioning analysis, drug tolerance and withdrawal symptoms are both manifestations of conditioned compensatory responses (Siegel and Ramos, 2002). These drug-compensatory responses are proposed to mediate the development of tolerance by counteracting the drug effect when administered in the context of usual drug-administration cues (which may also be interpreted as "drug preparation" symptoms). In contrast, if the drug is not administered in the presence of usual cues, the conditioned compensatory responses are not attenuated by drug effect and thus achieve full expression, increasing the risk of drug overdose. The essential role of gut microbiota in learning, memory, and stress highlights the striking impact of the gut in drug anticipation and craving (Sudo et al., 2004; Bravo et al., 2011; Diaz Heijtz et al., 2011; Desbonnet et al., 2015).

The finding that opioid tolerance to analgesia can be transferred via fecal transfer from an opioid-dependent mouse model into opioid-naive mice reveals that opioid exposure produces changes in gut bacteria that contribute to the development of tolerance to the pain-relieving effects of opioids (Kang et al., 2017; Lee et al., 2018; Yang et al., 2019). Gut microbiota diversity is in fact altered with chronic opioid use in humans and mice, and these changes alter neuronal tolerance in extrinsic sensory afferents (Akbarali and Dewey, 2017). In addition, the rate of tolerance to the analgesic effects of morphine is exaggerated in the presence of colonic inflammation (Komla et al., 2019).

While tolerance to the analgesic and rewarding properties of opioids develops rapidly, the gastrointestinal-related side effects, including pain, nausea, and constipation, remain consistent and often worsen with chronic opioid exposure (Akbarali and Dewey, 2017). One consideration is that gastrointestinal distress is one presentation of a conditioned compensatory response to opioid intake. As an example, diarrhea and/or vomiting are commonly observed signs of withdrawal, and administration of opioids alleviates these symptoms by inducing constipation and reduced gut motility. Gut dysbiosis may act as an interoceptive cue to opioid administration, similar to external cues, and elicit conditioned responses that mediate drug tolerance (Razran, 1961). Consistent with this hypothesis, tolerance can be prevented with a peripheral mu-opioid receptor antagonist, which supports a peripheral or gut mechanism mediating opioid tolerance (Komla et al., 2019). Furthermore, the insula integrates interoceptive states into emotions and conscious feelings, and its reactivity has been suggested to serve as a biomarker to predict relapse in humans (Naqvi and Bechara, 2009; Janes et al., 2010).

Possible mechanisms of the gut microbiome affecting opioid use behavior

Neuroinflammation

Gut-brain communication occurs vastly through immune pathways. Gut bacteria control the differentiation and function of immune cells in the brain, periphery, and intestines (Erny et al., 2015; Matcovitch-Natan et al., 2016; Rooks and Garrett, 2016), and a healthy intestinal lining forms a tight barrier to control what gets absorbed into the bloodstream. It is therefore feasible to expect that perturbed gut bacteria and/or structure prompt immune dysfunction by triggering inflammation throughout the brain and body.

Intestinal barrier integrity can be threatened by a Western-style diet, certain medications, stress, and autoimmune conditions (Gareau et al., 2007; Stewart et al., 2017), which cause the tight junctions in the large intestine to open up (i.e. leaky gut) and allow bacteria and their toxins to get through, eliciting a systemic inflammatory response. Neuroinflammation is characterized by increased microglial activation and/or malformed microglial morphology. Gut, brain, and systemic inflammation are seen in acute and chronic stress and mood disorders (Maes et al., 2012; Wohleb and Delpech, 2017), as well as in opioid-dependent states and particularly in states of withdrawal (Taylor et al., 2015; Lee et al., 2018). Neuroinflammation disrupts the function and projections of dopaminergic neurons within VTA, leading to decreased mesolimbic dopaminergic activity and dysregulated reward, which is a shared characteristic of chronic pain, depression, and opioid addiction (Taylor et al., 2015; Cahill and Taylor, 2017). Vulnerability to the negative effects of opioids may be heightened by inflammation, which can develop from chronic opioid use, creating a vicious cycle.

Microbial metabolites

Gut bacteria help break down certain nutrients, which can be further metabolized by host cells. Several of these products, short-chain fatty acids (SCFAs, e.g. butyric acid, propionic acid, and acetic acid), are associated with neural function. Gut bacteria also produce tryptophan, serotonin, dopamine, and GABA, which play important roles in the brain as neurotransmitters or their precursors (Lyte, 2011; Thomas et al., 2012; Wall et al., 2014; Sudo, 2019).

SCFAs are considered to be beneficial to the host due to their anti-inflammatory effects and epigenetics regulation (Tsankova et al., 2007; Kim et al., 2014; Emy et al., 2015; Stilling et al., 2016). SCFAs are able to influence memory and learning processes in the brain and alleviate stress (Chambers et al., 2015; J. Liu et al., 2015; Byrne et al., 2016; Amoldussen et al., 2017; Burokas et al., 2017; de Wouw et al., 2018; Garcez et al., 2018). Additionally, administration of SCFAs normalizes microglial abnormalities in germ-free mice (Erny et al., 2015) and reverses the enhanced reward sensitivity to cocaine seen in gut bacteria-depleted mice (Kiraly et al., 2016). Opioid-related behaviors may be due in part to reduced bacterial metabolism, which can be repleted with SCFA supplementation.

Serotonin (5-HT)

Microbiota can regulate 5-hydroxytryptamine (5-HT) synthesis in the gut, which is important given that dysfunctional 5-HT signaling may underlie symptoms of gastrointestinal and mood disorders (Yano et al., 2015). Peripherally, 5-HT is involved in pain perception and regulation of gut secretion and motility, and centrally, 5-HT signaling pathways are implicated in regulating mood and cognition (Gershon and Tack, 2007; O'Mahony et al., 2015). Gut bacteria may play a crucial role in tryptophan availability and metabolism to consequently impact central 5-HT concentrations (de Wouw et al., 2019). The relationship between gut bacteria, serotonin synthesis and signaling, and mood is imperative to note as a consideration in addiction and motivated behaviors.

Microbial diversity and presence of specific species

Dysbiosis is characterized by imbalances in bacterial species, which can be measured by total abundance, species ratios, alpha diversity, and/or the presence or absence of a specific species. An imbalance in the body's normal gut microbiota disrupts immunity and nutrition and leads to relative overgrowth of bacteria, which can progress into a secondary infection, such as the pathogenic *Clostridium difficile*. Gut microbiomes with high diversity are posited to be more beneficial to host health than low diversity microbiomes, as many different species exist in low numbers in a high diversity environment and expend more resources competing with other bacteria rather than manipulating the host (Alcock et al., 2014).

Specific bacterial species may exert immunomodulatory effects on the central nervous system. *Lactobacillus reuteri* (*L. reuteri*) decreases anxiety-like behavior and stress-induced increase of corticosterone in mice, and alters mRNA expression of both GABA-A and GABA-B receptors in the central nervous system (Bravo et al., 2011). Vagotomy in these animals prevents the anxiolytic and antidepressant effects of *L. reuteri*, which indicates that parasympathetic innervation is necessary for *L. reuteri* to participate in the microbiota-brain interaction. Further, many species of *Lactobacillus* and *Bifidobacterium* produce GABA; *Candida, Escherichia,* and *Enterococcus* produce serotonin; and some *Bacillus* species produce dopamine (Lyte, 2011; Barrett et al., 2012). Additional research on bacterial species differences in substance use disorder is necessary to understand the functions of specific species and for a precise therapeutic intervention in opioid use.

Conclusion

Few preclinical studies have directly examined the role of gut afferents and bacteria on addiction-like behavior (Kiraly et al., 2016; Han et al., 2018; Lee et al., 2018). Current perspectives focus on dysfunctional reward processing, stress, and mood disorders as risk factors, characteristics, and/or co-morbidities in addiction and their implications with gut dysbiosis. Different pathways mediate the pain-relieving and rewarding effects of opioids, so although an apparent relationship exists between gut bacteria and analgesic tolerance to opioids, further research is needed to evaluate how the gut microbiome modulates opioid reward and reinforcement.

We highlight here the role of gut bacteria in the affected neurocircuitry and behaviors of opioid abuse and addiction, including the stress HPA axis, mesolimbic dopamine system, tolerance, withdrawal, and craving. We also provide support that the gut-brain axis and opioid use share bidirectional communication, as opioid exposure changes the gut microbiome, and manipulation of gut bacteria influences opioid-related behaviors, such as pain tolerance, withdrawal, anhedonia, and drug reward. The impact of gut dysbiosis on impaired reward, enhanced stress, and neuroinflammation, as well as the glaring feedback of these factors on gut health, strongly implicates an important role of the gut-brain axis in opioid use.

Individual differences in gut microbiomes contribute to variations in drug metabolism, which account for the disparities in therapeutic efficacy and side effects between individuals (Zimmermann et al., 2019). An interesting, targeted approach to personalized medicine would be to modulate or supplement the gut microbiota to increase the efficacy of a drug or reduce its adverse effects. Our knowledge of the gut microbiome on obesity has led to clinical trials to evaluate benefits of FMT in non-gastrointestinal disorders, including obesity (Carlucci et al., 2016; Jayasinghe et al., 2016), autism (Kang et al., 2017), multiple sclerosis (Makkawi et al., 2018), and depression (Wortelboer et al., 2019). A further understanding of the role of the gut microbiome in drug addiction and opioid use may offer a novel targeted approach in the treatment of substance use disorders and/or a combined therapy with opioid regimens.

Acknowledgments

Funding: This work was supported by the University of California Irvine (UCI) Microbiome Initiative Pilot Grant Program (SL), UCI School of Medicine start up fund (SL), UCI Institute for Clinical and Translational Sciences (ICTS) Pilot Studies Program (NUT/NCATS) (SL), Helping End Addiction Long-Term (HEAL) Initiative Opioid-Related Pilot Studies Program (ICTS, UCI School of Medicine, Department of Anesthesiology and Perioperative Care) (SL), UCI Department of Emergency Medicine Pilot Award (SL), and UCI Center for the Neurobiology of Learning and Memory Pedagogical Fellowship (MR).

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