OXFORD

International Journal of Neuropsychopharmacology (2023) 26(1): 70–79

https://doi.org/10.1093/ijnp/pyac060
Advance Access Publication: September 10, 2022
Review

REVIEW

Cyclic Nucleotide Phosphodiesterases in Alcohol Use Disorders: Involving Gut Microbiota

Xueqin Hou*, Cuiping Rong*, Qiwei Zhang, Shuangshuang Song, Yifan Cong, and Han-Ting Zhang

Institute of Pharmacology, Shandong First Medical University and Shandong Academy of Medical Sciences, Taian, Shandong 271016, P.R. China (Drs Hou, Zhang, Song, and Cong); The Second School of Clinical Medicine, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510006, P.R. China (Dr Rong); Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, 266073, P.R. China (Dr Zhang).

*These authors contributed equally. Correspondence: Xueqin Hou, PhD, Institute of Pharmacology, Shandong First Medical University & Shandong Academy of Medical Sciences, Taian, Shandong 271016, P.R. China (houxueqin09@126.com) and Han-Ting Zhang, MD, PhD, Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, Shandong 266073, P.R. China (htzhang@qdu.edu.cn).

Abstract

Alcohol abuse is 1 of the most significant public health problems in the world. Chronic, excessive alcohol consumption not only causes alcohol use disorder (AUD) but also changes the gut and lung microbiota, including bacterial and nonbacterial types. Both types of microbiota can release toxins, further damaging the gastrointestinal and respiratory tracts; causing inflammation; and impairing the functions of the liver, lung, and brain, which in turn deteriorate AUD. Phosphodiesterases (PDEs) are critical in the control of intracellular cyclic nucleotides, including cyclic adenosine monophosphate and cyclic guanosine monophosphate. Inhibition of certain host PDEs reduces alcohol consumption and attenuates alcohol-related impairment. These PDEs are also expressed in the microbiota and may play a role in controlling microbiota-associated inflammation. Here, we summarize the influences of alcohol on gut/lung bacterial and nonbacterial microbiota as well as on the gut-liver/brain/lung axis. We then discuss the relationship between gut and lung microbiota-mediated PDE signaling and AUD consequences in addition to highlighting PDEs as potential targets for treatment of AUD.

Keywords: Cyclic nucleotide phosphodiesterase, PDE, alcohol use disorder, AUD, gut microbiota

Introduction

Alcohol dependence and abuse cause serious social problems and economic consequences all over the world (Witkiewitz et al., 2019). Chronic heavy alcohol use and loss of control over alcohol intake lead to alcohol use disorder (AUD) (Carvalho et al., 2019). As the second messengers in the organism, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) mediate biological effects triggered by extracellular signals such as hormones and neurotransmitters, which in turn regulate various cellular functions. Phosphodiesterases (PDEs) are enzymes that regulate the intracellular levels of cAMP and cGMP. In recent years, PDE-mediated cAMP and cGMP signaling in the brain is considered important in alcohol drinking behavior (Blednov et al., 2014; Logrip et al., 2014; Shi et al., 2018; Wen et al., 2018). In addition to AUD, excessive alcohol consumption damages the intestine, changes gut microbiota, and impairs liver and lung function, which in turn deteriorate AUD. Human microbiota, which consists of bacterial and nonbacterial microbiomes such as fungi, archaea, and viruses (Bajaj, 2019), is widely distributed within various body habitats, including the digestive system, respiratory system, vagina,

Received: December 27, 2021; **Revised:** August 18, 2022; **Accepted:** September 9, 2022

and the skin (Human Microbiome Project Consortium, 2012). Growing evidence shows that gut microbiota is affected by alcohol (Bjørkhaug et al., 2019; Lamas-Paz et al., 2020; Mutlu et al., 2012; Posteraro et al., 2018). Moreover, PDEs are involved in the regulation of microbiota functions (Matange, 2015). Thus, microbiota-associated PDE signaling may be a potential target for modulating alcohol-related disorders.

Alcohol Alters Gut and Lung Microbiota

We conducted a PubMed search for the relevant literature by using 2 sets of terms—*alcohol* (including *alcohol, ethanol,* and *alcohol use disorder*) and *microbiota* (including *microbiota, microbiome, bacteria, fungi,* and *viruses*)—and narrowing the language to articles published in English. Then, we further screened the retrieved articles for review if they were associated with the topic "effects of alcohol on the gut microbiota." Bacterial microbiota and nonbacterial microbiota were summarized separately and included both human and animal studies.

Bacterial Microbiota—Alcohol consumption alters the diversity and composition of the microbiota within the digestive and respiratory systems. Human studies have found that higher alcohol consumption decreases the abundance of the commensal order Lactobacillales and increases certain genera (eg, *Actinomyces*, *Leptotrichia*, *Cardiobacterium*, and *Neisseria*) of the oral microbiota (Fan et al., 2018). Animal studies have shown, however, that the Lactobacillales order is higher in alcohol-fed mice (Shimizu et al., 2016). People with AUD have higher subgingival microbiota, including *Aggregactibacter actinomycetemcomitans, Fusobacterium nucleatum,* and *Porphyromonas gingivalis* (da Silva Furtado Amaral et al., 2011). Alcohol consumption is also associated with alterations of the esophageal microbiota, which covers various orders (eg, Clostridiales, Gemellales, and Pasteurellales), families (eg, Clostridiaceae, Lanchnospiraceae, and Helicobacteraceae), genus (eg, *Clostridium, Helicobacter, Catonella,* and *Bacteroides*), and species (Rao et al., 2021). In addition, patients who engage in excessive alcohol consumption have more fecal microbiota from Proteobacteria; higher levels of *Sutterella, Holdemania,* and *Clostridium;* but fewer bacteria from *Faecalibacterium* and *Bacteroidetes* (Bjørkhaug et al., 2019; Mutlu et al., 2012). As with the oral consumption of alcohol, exposure to chronic intermittent vaporized ethanol alters the gut microbiota in mice (Peterson et al., 2017), which changes rapidly following abstinence from alcohol (Ames et al., 2020). In addition to the digestive tract, the AUD population also shows increases in α-diversity of the oropharyngeal, bronchial mucosa, and distal lung alveolar microbial communities. The relative abundance of specific (eg, *Neisseria*, *Porphyromonas*, *Actinobacillus*) and Gram-negative taxa (eg, *Haemophilus*, *Prevotella*) were significantly increased in participants with AUD, suggesting that AUD is associated with alteration of the microbial composition in the respiratory tract (Samuelson et al., 2018).

The diversity and composition of the microbiota differ depending on the level of alcohol consumption and the location of the habitats. Heavy drinkers tend to have a lower α-diversity; less abundance of *Subdoligranulum*, *Roseburia*, and *Lachnospiraceaeunc91005*; but greater abundance of *Lachnospiraceaeunc8895*, while light drinkers have greater abundance of *Akkermansia* (Gurwara et al., 2020). Patients with AUD often have a decreased α-diversity of microbiota. The increase in *Bacteroides* and decrease in *Akkermansia* helps identify participants with AUD with high accuracy (Addolorato et al., 2020). Chronic alcohol consumption changes the microbiota composition in the colon but not the microbiota diversity in the jejunum and colon in rats (Yang et al., 2018). Another study indicates that chronic alcohol intake has dramatic effects on the microbiota composition in the ileum in mice (Bluemel et al., 2020).

Alcohol consumption alters the metabolism of the colonic microbiota evaluated by the 13C-D-xylose breath test in participants, where the time curves of $^{13}CO_2$ excretion at 90 to 240 minutes reflects colonic microbial metabolism (Bjørkhaug et al., 2017). Fatty acid is 1 type of metabolite of the gut microbiota, including long- and short-chain fatty acids. Saturated long-chain fatty acids are metabolized by commensal *Lactobacillus,* which in turn promotes their growth (Chen et al., 2015b). The biosynthesis of saturated long-chain fatty acids can be inhibited by chronic intake of alcohol (Chen et al., 2015b). Furthermore, patients who overuse alcohol have decreased short-chain fatty acids, such as the butyric acid (Bjørkhaug et al., 2019). In rats, following 8 weeks of alcohol exposure, short-chain fatty acids—including propanoic acid, 2-methyl-propanoic acid, butyric acid, 2-methyl-butyric acid, 3-methyl-butyric acid, and heptanoic acid—are decreased, though acetic acid is elevated because it is a product of ethanol metabolism (Xie et al., 2013). The *Lactobacillus* mixture modulates the gut microbiota and increases short-chain fatty acid products (Li et al., 2021). Short-chain fatty acids are important energy sources, and the receptor GPR43 links the metabolic activity of the gut microbiota with host body energy homoeostasis (Kimura et al., 2013).

In addition to fatty acids, chronic alcohol exposure decreases amino acids and branched-chain amino acids, increases steroids, and alters bile acids in rats (Xie et al., 2013). *Bacteroides*, a symbiotic bile tolerance genus involved in bile acid metabolism, is 1 of the main bacteria-producing γ-aminobutyric acid (GABA); the GABA-glutamate pathway leads to the enhancement of the gut microbiota of patients with AUD. GABAergic/glutamatergic disorders may play a role in alcohol addiction and the development and maintenance of AUD (Addolorato et al., 2005; Fujisaka et al., 2018). Alcohol not only enhances the central inhibitory effect of GABA by increasing the release of GABA or acting on $GABA_A$ postsynaptic receptors but also induces the intestinal flora imbalance phenotype of the GABAergic system. The gut microbiota associated with AUD also increases GABA metabolic pathways (Addolorato et al., 2020).

The altered gut microbiota correlates with the levels of endotoxins and inflammatory factors in some subsets of people with alcoholism (Mutlu et al., 2012). Lipopolysaccharides (LPS) and peptidoglycans are 2 endotoxins from the gut microbiota. They can cross the gut barrier to enter the systemic circulation and activate toll-like receptors (TLRs) in peripheral blood mononuclear cells (Leclercq et al., 2014b). The levels of LPS in the serum are increased in patients with AUD (Addolorato et al., 2020). Furthermore, patients with alcohol overuse display increases in systemic inflammatory activity. Chronic alcohol consumption inhibits the proinflammatory cytokine nuclear factor-κB and activates the mitogen-activated protein kinase/activator protein 1 and inflammasome complex, leading to increases in interleukin-8 (IL-8) and IL-1β (Leclercq et al., 2014b). Patients with alcohol overuse also have higher levels of other proinflammatory cytokines, including tumor necrosis factor α (TNF-α), monocyte chemoattractant protein 1, IL-6, and interferon-γ (IFN-γ), and lower levels of anti-inflammatory cytokine transforming growth factor β1 (Addolorato et al., 2020; Bjørkhaug et al., 2020). Of the above-mentioned factors, IFN-γ, is involved in the regulation of antimicrobial peptides by modulating STAT1 and STAT3 (Yue et al., 2021). Thus, impaired IFN-γ–STAT signaling may contribute to the alcohol-induced microbial dysbiosis. Taken together, alcohol-induced changes in gut microbiota are associated with proinflammatory profiles.

Nonbacterial Microbiota—Chronic alcohol consumption causes alcohol-related liver disease by increasing intestinal permeability and changing the intestinal microbiota composition. In addition to the bacterial microbiota, commensal fungi in the gut contribute to the development of alcohol-related liver disease (Gao et al., 2021b). In patients with alcoholic hepatitis and AUD, the fungal diversity is lower and *Candida* overgrows (Gao et al., 2021a; Hartmann et al., 2021; Lang et al., 2019; Yang et al., 2017). Of the *Candida* genera, the abundance of *Candida albicans* and *Candida zeylanoides* species are increased in AUD (Hartmann et al., 2021). Furthermore, patients with AUD show increased abundance of other genera, including *Debaryomyces, Pichia, Kluyveromyces,* and *Issatchenkia* (Hartmann et al., 2021). Apart from the fungi, it has been found that patients with alcoholic hepatitis show increased viral diversity in fecal samples, with over-representation of *Escherichia-, Enterobacteria-,* and *Enterococcus* phages, and increases in mammalian viruses (Parvoviridae and Herpesviridae) (Jiang et al., 2020). These findings suggest that nonbacterial microbiota plays a potential role in alcohol-related liver disease.

Chronic alcohol use increases translocation of fungal β-glucan into systemic circulation. When β-glucan enters the liver, it can bind to the C-type lectin domain family 7 member A (CLEC7A, or Dectin-1) on Kupffer cells, subsequently increasing the expression and secretion of IL-1β and eventually resulting in liver inflammation and the development of alcohol-induced liver disease (Yang et al., 2017). Therefore, regulating intestinal fungal dysbiosis and inhibiting the Dectin-1/IL-1β signaling pathway can ameliorate alcohol-related liver injury (Wu et al., 2020). Moreover, the CLEC7A-independent pathway contributes to alcohol-associated liver disease. Candidalysin is a toxin secreted by *C albicans*, the number of which is increased in the feces of patients with alcoholic hepatitis (Chu et al., 2020). Candidalysin triggers epithelial cellular stress, leading to necrotic death (Blagojevic et al., 2021). It also damages hepatocytes directly and enhances alcohol-associated liver disease independent of CLEC7A (Chu et al., 2020). Furthermore, *C albicans* may interact with immune cells in the intestines through TLR2 and TLR4 (Li et al., 2018). Gut fungi (*Meyerozyma guilliermondii*) also induce production of prostaglandin 2 in the liver, which may be associated with alcoholic hepatic steatosis (Sun et al., 2020). Thus, inflammation triggered by gut fungi may be 1 of the mechanisms in alcohol-induced liver disease. Interestingly, *Lactobacillus rhamnosus* moderates intestinal injury by reducing gut *Candida* and improves intestinal bacterial conditions (Panpetch et al., 2021). In patients with alcoholic hepatitis, both positive association (*Cladosporium* and *Gemmiger*) and negative association (*Cryptococcus* and *Pseudomonas*) have been found between fungi and bacteria (Gao et al., 2021a), suggesting the interaction between the gut bacterial microbiota and nonbacterial microbiota. Therefore, alcohol may interrupt the microbiota balance, resulting in liver inflammation and alcohol-related liver diseases.

Alcohol Alters the Gut-Liver/Brain/Lung Axis

In this section, we used 3 sets of search terms—*alcohol* (including *alcohol, ethanol,* and *alcohol use disorder*), *gut* (including *gut, microbiota, bacteria, fungi,* and *viruses*), and *liver/brain/lung*—to perform literature searches in PubMed. Those articles that were published in English and met the topic "alcohol alters the gut-liver/brain/lung axis" were included for review.

The Gut-Liver Axis—Alcohol affects the cross-talk between gut microbiota and the liver. In patients with severe alcoholic hepatitis, the diversity of microbiota is changed (Kim et al., 2021), more specifically, with *Akkermansia* decreased while *Veillonella* increased (Lang et al., 2020). Alcohol abstinence causes different microbial responses in patients with AUD, with different degrees of hepatic steatosis (Gao et al., 2020). In germ-free mice, alcohol consumption causes only mild neutrophil infiltration and proinflammatory cytokine levels in the liver, with no liver injury (Canesso et al., 2014). This finding appears to be contradicted by another study, however, that demonstrates that germ-free mice have greater liver injury and inflammation after alcohol intake (Chen et al., 2015a). The absence of microbiota also increases hepatic expression of alcohol-metabolizing enzymes (Chen et al., 2015a). Mice harboring the intestinal microbiota from patients with severe alcoholic hepatitis have more severe liver inflammation (Llopis et al., 2016). These findings suggest that gut microbiota affects liver function.

Excessive consumption of alcohol changes the circulating microbiome and may lead to severe alcoholic hepatitis (Ciocan et al., 2018; Llopis et al., 2016; Puri et al., 2018). In addition, alcohol dependence and relevant liver dysfunction influence the gut microbiota negatively (Dubinkina et al., 2017). The microbiota changes, in turn, may result in bacterial translocation to the liver (Bluemel et al., 2020), leading to increased liver injury. Alcohol reduces claudin-1, intestine trefoil factor, P-glycoprotein, and cathelin-related antimicrobial peptide in the ileum and increases their transcription factor hypoxia-inducible factor-2α, leading to increased intestinal permeability and endotoxemia (Wang et al., 2012b). The intestinal epithelial and vascular permeability influences fecal microbiota dysbiosis (Maccioni et al., 2020). Interestingly, *L rhamnosus* GG culture supernatants can suppress the alcohol-induced intestinal impairment and subsequently liver injury (Wang et al., 2012b). Thus, regulating the gut microbiota is a potential strategy to treat the alcoholic liver injury. In patients with alcoholic hepatitis, oral supplementation with the cultured L form of *Bacillus subtilis/Streptococcus faecium* improves liver function and decreases TNF-α and *Escherichia coli* levels (Han et al., 2015). Oral intestinal alkaline phosphatase supplementation or intestinal microbiota manipulation could prevent alcohol-induced liver injury by decreasing endotoxins, maintaining immune homeostasis, and reducing inflammation (Hamarneh et al., 2017; Llopis et al., 2016; Tian et al., 2020; Yu et al., 2020).

Chronic excessive alcohol intake causes liver injury, which in turn disturbs the balance of microbiota. Alcohol produces damage to the liver and colon and changes the levels of bile acid, secondary bile acid, serotonin, and taurine (Hartmann et al., 2018; Wang et al., 2018). Bile acids are molecules produced by the liver; they play a role through its receptor, TGR5. Deficiency of TGR5 results in microbiota dysbiosis and worsens alcohol-induced liver injury (Spatz et al., 2021). In addition, bile acid-FXR-FGF15 signaling may be involved in alcohol-induced liver disease (Hartmann et al., 2018), indicating that bile acid can be an important modulator in alcohol-induced liver injury.

The Gut-Brain Axis—Gut microbiota is involved in regulating brain functions and behaviors, which are changed by chronic alcohol exposure. Gut microbiota composition contributes to alcohol withdrawal–induced anxiety (Xiao et al., 2018). The alteration of gut microbiota increases the possibility of developing depression, anxiety, and alcohol craving (Leclercq et al., 2014b; Rodriguez-Rabassa et al., 2020), which are related to the changes in proinflammatory cytokines and anti-inflammatory cytokine, such as LPS, IL-6, and IL-10 (Leclercq et al., 2012; Rodriguez-Rabassa et al., 2020). Intestinally derived LPS, which

is ubiquitous in the gut lumen, increases anxiety-like behavior in mice, most likely by regulating the TLR4 pathway (Fields et al., 2018). Interestingly, fecal microbiota transplant reduces alcohol craving and AUD-related events (Bajaj et al., 2021). This finding is consistent with the findings that the microbiota is involved in alcohol-induced anxiety and depression, probably through regulating brain-derived neurotrophic factor, the α-1 subunit of $GABA_A$ receptors, metabotropic glutamate receptor 1, and protein kinase C ε in specific brain areas (Xu et al., 2019; Zhao et al., 2020). In addition, the vagus nerve links the gut microbiota information to the brain, which can account for bilateral vagotomy-induced drastic inhibition of alcohol intake in rats (Ezquer et al., 2021). Therefore, the effect of alcohol can be mediated through the gut-vagus-brain axis. Because the gut microbiota is importantly involved in the development of alcohol-associated brain dysfunction, transplantation of fecal microbiota could be an approach to treatment of alcohol-induced anxiety and depression (Xu et al., 2018). Antibiotic treatment also prevents chronic intermittent alcohol intake–induced depression-like behavior and the increase in kynurenine in the limbic forebrain (Giménez-Gómez et al., 2019).

Short-chain fatty acids are microbial metabolites that have various effects in brain disorders. For example, microbial short-chain fatty acids alleviate stress-induced brain-gut axis alterations (van de Wouw et al., 2018), promote poststroke recovery in aged mice (Lee et al., 2020), modulate microglia, promote Aβ plaque deposition (Colombo et al., 2021), and contribute to neuropathic pain (Zhou et al., 2021). The roles of short-chain fatty acids in gut-brain communication have been reviewed recently (Dalile et al., 2019; Silva et al., 2020). In addition to short-chain fatty acids, gut bacterial microbiota–derived peptidoglycan can be translocated into the brain and sensed by specific pattern-recognition receptors of the innate immune system (Arentsen et al., 2017). After entering the brain, peptidoglycan induces inflammation and neurotoxicity in mice (Arroyo et al., 2018). Hence, gut bacterial microbiota can affect brain function through short-chain fatty acids and peptidoglycan. In addition to the bacterial microbiota metabolites, fungal toxin candidalysin carries another potential risk of brain disorders. Candidalysin induces neutrophil-recruiting production of IL-1β and CXCL1 in microglial cells (Drummond et al., 2019). Taken together, gut microbiota–secreted factors are mediators in gut-brain communication.

The Gut-Lung Axis—It has been recognized that alcohol abuse increases the risk of pneumonia and acute respiratory distress syndrome (Kershaw and Guidot, 2008; Moss and Burnham, 2003). In bronchoalveolar lavage fluid from humans with acute respiratory distress syndrome, gut-specific bacteria *Bacteroides* species are enriched, which is correlated with the intensity of systemic inflammation (Dickson et al., 2016), suggesting the existence of gut-lung cross-talk. Gram-negative taxa in the respiratory tract of individuals with AUD have been shown to be significantly increased (Samuelson et al., 2018). The retained bacterial products (eg, LPS) may increase pulmonary inflammation, which may in turn benefit the alcohol-associated bacterial pathogens (*Streptococcus pneumoniae, Klebsiella pneumoniae,* and *Legionella pneumophilia*) (Samuelson et al., 2018). Gut microbiota dysbiosis can induce outgrowth of opportunistic pathogens, which contributes to chronic inflammation at distal sites (Budden et al., 2017). Animal studies have also demonstrated that alcohol-induced dysbiosis increases host susceptibility to *K pneumonia* (Samuelson et al., 2017). Collectively, alcohol-associated dysbiosis is a risk factor for respiratory inflammation.

Host PDEs for Treating AUD

In eukaryotes, PDEs have 11 families (PDE1-11), some of which consist of 2 to 4 subtypes. Most of the PDEs are highly or moderately expressed or at least detectable in the brain, such as PDE1, PDE2, PDE4, and PDE9 (Lakics et al., 2010; Perez-Torres et al., 2000; Reyes-Irisarri et al., 2007). To date, approved treatments for AUD are still limited in clinic, although many clinical trials have been conducted for more potential medications for alcohol dependence or AUD. Recently, pharmacotherapies for AUD have been reviewed in various publications (Castrén et al., 2019; Kranzler and Soyka, 2018; Palpacuer et al., 2018). To update the recent advances in clinical trials of pharmacological treatment for AUD, we conducted a PubMed search using the key words *alcohol use disorder* and *clinical trial,* narrowing the time window from January 2019 to December 2021 and restricting the language of publication to English. Of the 8 studies that met the criteria for clinical trials of pharmacotherapy for AUD (Anton et al., 2020; Brown et al., 2019a; Burnette et al., 2021; Coker et al., 2020; Falk et al., 2019; Garbutt et al., 2021; Grodin et al., 2021; Mariani et al., 2021), 2 focused on ibudilast, a nonselective PDE inhibitor that inhibits PDE3, 4, 10, and 11. Ibudilast has been shown to produce potential effects in the treatment of AUD, including reduction in alcohol drinking and improvement of mood (Grodin et al., 2021; Ray et al., 2017), indicating that host cyclic nucleotide PDEs are potential targets for the treatment of AUD.

In the human liver, all PDEs except for the PDE6 can be detected. Similarly, the messenger RNA (mRNA) of PDE1 through 5 and PDE7 through 10 are expressed in the human lung (Lakics et al., 2010). Moreover, it has been shown that PDE inhibitors have beneficial effects in patients with liver or lung diseases. For instance, the PDE4 inhibitor roflumilast can safely be used in patients with mild and moderate liver cirrhosis (Hermann et al., 2007); the PDE4B inhibitor BI 1015550 prevents a decrease in lung function in patients with idiopathic pulmonary fibrosis (Richeldi et al., 2022). More studies are needed, however, to determine whether PDE inhibitors are beneficial to patients with AUD-associated liver or lung diseases.

Microbiota-Related PDE Signaling: A Potential Role in AUD Consequences

PDE Expression in the Microbiota—In addition to the eukaryote, PDEs are also present in the prokaryote (Matange, 2015). For instance, Rv0805, a PDE found in *Mycobacterium tuberculosis* (Malhotra and Chakraborti, 2016), has most recently been identified and found to reduce cAMP levels, impair bioenergetics, and disrupt peptidoglycan biosynthesis (Thomson et al., 2022). In addition to cAMP hydrolysis, mycobacterial PDE is involved in regulating cell wall permeability (Podobnik et al., 2009). CpdA is a cAMP PDE identified from *E coli* (Imamura et al., 1996; Matange, 2015). It is also expressed in *Vibrio vulnificus* and *Pseudomonas aeruginosa* (Fuchs et al., 2010; Kim et al., 2009). In *V vulnificus* (a pathogenic bacterium), CpdA, which catalyzes the conversion of cAMP to AMP, is activated by the cAMP-cAMP receptor protein complex (Kim et al., 2009). In *P aeruginosa,* intracellular cAMP accumulation increased following the deletion of CpdA (Fuchs et al., 2010). Similar to cAMP and cGMP, c-di-AMP and c-di-GMP are 2 important second messengers found in bacteria, and they are degraded by PDEs. It has been known that rmdB encodes a PDE for c-di-GMP hydrolysis. In *Streptomyces albus,* inactivation of rmdB positively correlates with c-di-GMP and moenomycin A accumulation (Makitrynskyy et al., 2020). Taken together, microbiota-associated PDEs play important roles in regulating

cell wall permeability and virulence, which may further affect the level of inflammation.

Microbiota PDE-Associated Signaling in AUD Consequences—PDE signaling plays an important role in AUD and microbiota, making it a potential mediator to link the microbiota and AUD. As discussed earlier, the metabolites and growth of gut microbiota are associated with AUD. In the following section, we summarize the relationship between microbiota-related PDE signaling and AUD consequences. We performed literature searches in PubMed by using 2 sets of search terms: *PDE signaling* (including *phosphodiesterase, cyclic nucleotide, cAMP,* and *cGMP*) and *microbiota* (including *microbiota, bacteria,* and *fungi*)/*microbiota metabolite* (including *fatty acid, lipopolysaccharide, peptidoglycans, β-glucan,* and *candidalysin*). The articles published in English that met the topics were selected for review.

PDEs catalyze the hydrolysis of cAMP and cGMP, which can be triggered by external stimuli and signals. Cyclic nucleotides are involved in the biological effects of various organisms, including the microbiota. Both bacterial and nonbacterial types of microbiota can mediate the host environment through cAMP signaling (McDonough and Rodriguez, 2012). In bacteria, cAMP/cGMP signaling is part of the defense system (Cohen et al., 2019). In recent years, the role of cAMP in regulating the microbiota has been supported by increasing evidence. Given that some PDEs regulate intrabacterial cAMP levels (Matange, 2015), PDEs may play an essential role in the mediation of alcohol dependence and abuse through the control of intracellular levels of cyclic nucleotides.

The mucosal barrier is essential for gut integrity: It prevents microorganisms and toxins from entering the systemic circulation. Studies have shown that the PDE3 inhibitor olprinone reduces gut mucosal injury and portal endotoxin levels (Satoh et al., 2003). PDE4B can drive acute and chronic inflammation, which is exacerbated by gut dysbiosis and endotoxemia (Myers et al., 2019). During enterotoxigenic *E coli* infection, PDE5 restricts intracellular cGMP accumulation (Foulke-Abel et al., 2020). These studies suggest that the gut microbiota regulates inflammation partly through PDEs signaling. The gut microbiota generates the short-chain fatty acids butyrate and propionate, which activate intestinal gluconeogenesis gene expression through the cAMP-dependent pathway and the gut-brain neural circuit involving the free fatty acid receptor 3, respectively (De Vadder et al., 2014). In addition, butyrate activates cAMP–protein kinase A (PKA)–cAMP response element-binding protein signaling (Wang et al., 2012a), while free fatty acid receptor 3 modulates cAMP (Mizuta et al., 2020). Therefore, the effect of short-chain fatty acids on cAMP signaling plays a potential role in the gut-brain axis. An endotoxin from the gut microbiota, LPS induces Pde4b2 mRNA expression without changing Pde4a or Pde4d in mouse macrophage cells (Gobejishvili et al., 2011). Because alcohol changes the metabolites and products of the gut microbiota (Bjørkhaug

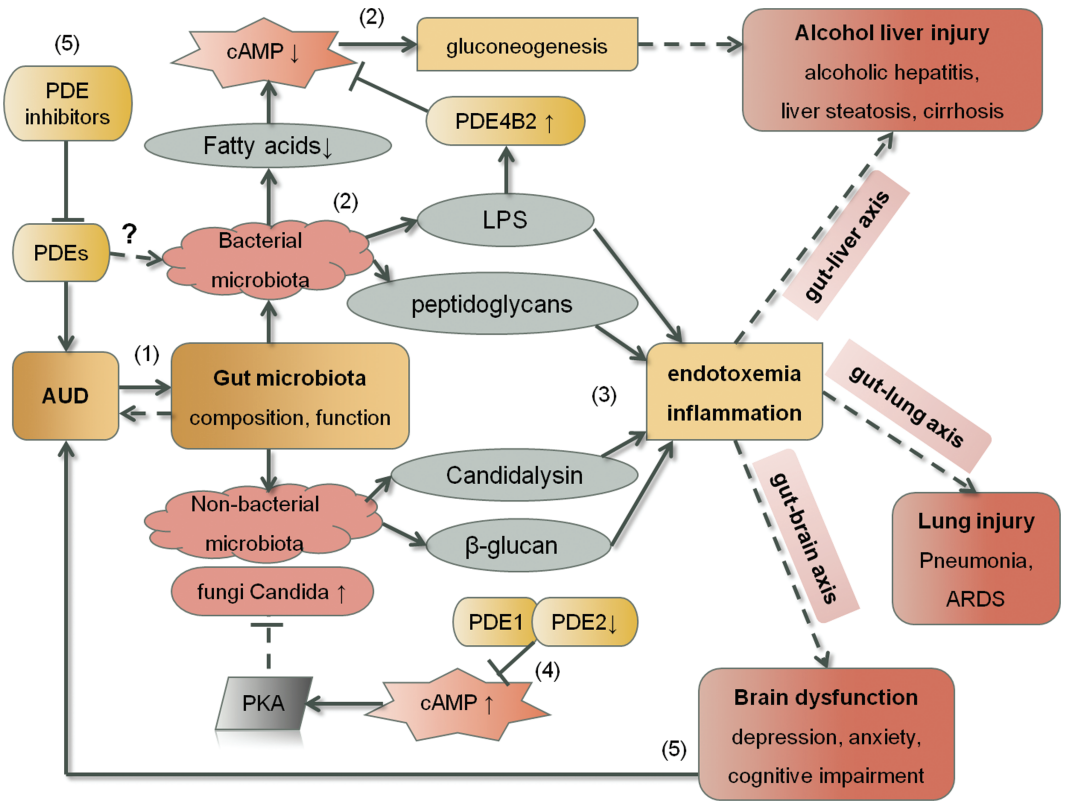

Figure 1. Alcohol use disorder (AUD) produces dysfunction of the liver, lung, and brain through the gut-liver/lung/brain axis, respectively. Excessive alcohol consumption changes the gut microbiota, including bacterial and nonbacterial types. Fatty acids from bacterial microbiota are involved in intestinal gluconeogenesis through cyclic adenosine monophosphate (cAMP) signaling, which is impaired by lipopolysaccharides (LPSs) by upregulating phosphodiesterase (PDE) 4B2, leading to further changes in intestinal gluconeogenesis. Productions of bacterial microbiota (LPS and peptidoglycans) and nonbacterial microbiota (β-glucan and Candidalysin) cause endotoxemia and inflammation, resulting in alcohol liver/lung injury and brain dysfunction. PDE1 and PDE2 regulate nonbacterial microbiota through cAMP signaling. Gut microbiota–related brain dysfunction may lead to higher alcohol intake and preference. Treatment with PDE inhibitors not only improves AUD but promotes the balance and compositions of gut microbiota, as well, which in turn further benefits AUD through the gut-liver, gut-lung, and gut-brain axes. ARDS, acute respiratory distress syndrome; PKA, protein kinase A.

et al., 2017), it is possible that microbiota-mediated PDE–cAMP signaling plays a role in the mediation of AUD.

As discussed earlier, patients with AUD have overgrowth of the fungus *Candida* (Lang et al., 2019; Yang et al., 2017). Thus, modulating *Candida* may be a potential strategy to reduce alcohol-associated liver injury. *C albicans* is 1 type of *Candida* that is changed by alcohol. It has been demonstrated that the Ras-cAMP-PKA pathway of *C albicans* is important for replication, survival, and microcolony formation (Kumar et al., 2020; She et al., 2020). The reduction of intracellular cAMP suppresses *C albicans* filamentation (Li et al., 2020). Pde1 and Pde2 are components of the Ras-cAMP-PKA pathway in *C albicans* (Huang et al., 2019). Deletion of PDE2 changes cellular walls and membranes of *C albicans* and affects stress responses and virulence (Jung et al., 2005; Wilson et al., 2007). Also, cAMP signaling controls fungal dimorphic switching and pathogenicity (Bores-Walmsley and Walmsley, 2000) and regulates development and virulence of fungi (D'Souza and Heitman, 2001). The increased expression of the *PDE2* gene in germ tubes not only inhibits CAP1-dependent synthesis of cAMP and hypha production but also promotes the virulence of *C albicans* (Bahn et al., 2003). Moreover, the interaction of PDE1 (and in some cases, PDE2) with GPA2 affects the growth, morphogenesis, and responses to some stresses of *C albicans* (Wilson et al., 2010). In addition to the growth of fungi, Pde1 and Pde2 play roles in bacterial growth (Bai et al., 2013). Taken together, PDE-cAMP signaling is a potential modulator involved in the function of the gut microbiota, which further mediates alcohol-induced disorders.

Conclusions

Excessive alcohol consumption not only causes AUD but also abnormally changes the gut and lung microbiota, which further causes dysfunctions of the liver, lung, and brain. PDE-cAMP signaling mediated by gut microbiota, both bacterial and nonbacterial, plays an important role in the mediation of alcohol-related disorders (Figure 1). Treatment with PDE inhibitors improves AUD, and they are effective in treating AUD-associated diseases through promotion of the balance and composition of gut microbiota, which in turn further benefits AUD via 3 axes: the gut-liver, gut-lung, and gut-brain axes. Unfortunately, the discussion on this point cannot be comprehensive because the literature on microbiota-related PDE signaling in AUD is limited. Further studies are needed to better understand the mechanisms of microbiota-mediated PDE signaling in AUD.

Acknowledgments

None.

Funding

This work was supported by grants from the National Natural Science Foundation of China (81773717 and 82073827), the Key Program of Brain Science and Brain-Like Intelligence Technology of the China Ministry of Science and Technology (2021ZD0202904), the Academic Promotion Program of Shandong First Medical University (2019QL011), the Key Project by Qingdao Bureau of Sciences and Technology (22-3-3-hygg-25-hy), the School Visit Project of Young Mentors in Shandong Province, and the Open Project Program of Guangxi Key Laboratory of Brain and Cognitive Neuroscience, Guilin Medical University (GKLBCN-202206-01).

Conflict of Interest

The authors declare no conflicts of interest.

References

Addolorato G, Leggio L, Abenavoli L, Gasbarrini G; Alcoholism Treatment Study Group (2005) Neurobiochemical and clinical aspects of craving in alcohol addiction: a review. Addict Behav 30:1209–1224.

Addolorato G, Ponziani FR, Dionisi T, Mosoni C, Vassallo GA, Sestito L, Petito V, Picca A, Marzetti E, Tarli C, Mirijello A, Zocco MA, Lopetuso LR, Antonelli M, Rando MM, Paroni Sterbini F, Posteraro B, Sanguinetti M, Gasbarrini A (2020) Gut microbiota compositional and functional fingerprint in patients with alcohol use disorder and alcohol-associated liver disease. Liver Int 40:878–888.

Ames NJ, Barb JJ, Schuebel K, Mudra S, Meeks BK, Tuason RTS, Brooks AT, Kazmi N, Yang SN, Ratteree K, Diazgranados N, Krumlauf M, Wallen GR, Goldman D (2020) Longitudinal gut microbiome changes in alcohol use disorder are influenced by abstinence and drinking quantity. Gut Microbes 11:1608–1631.

Anton RF, Latham P, Voronin K, Book S, Hoffman M, Prisciandaro J, Bristol E (2020) Efficacy of gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms a randomized clinical trial. JAMA Intern Med 180:728–736.

Arentsen T, Qian Y, Gkotzis S, Femenia T, Wang T, Udekwu K, Forssberg H, Heijtz RD (2017) The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior. Mol Psychiatry 22:257–266.

Arroyo DS, Gaviglio EA, Peralta Ramos JM, Bussi C, Avalos MP, Cancela LM, Iribarren P (2018) Phosphatidyl-inositol-3 kinase inhibitors regulate peptidoglycan-induced myeloid leukocyte recruitment, inflammation, and neurotoxicity in mouse brain. Front Immunol 9:770.

Bahn YS, Staab J, Sundstrom P (2003) Increased high-affinity phosphodiesterase PDE2 gene expression in germ tubes counteracts CAP1-dependent synthesis of cyclic AMP, limits hypha production and promotes virulence of *Candida albicans*. Mol Microbiol 50:391–409.

Bai Y, Yang J, Eisele LE, Underwood AJ, Koestler BJ, Waters CM, Metzger DW, Bai G (2013) Two DHH subfamily 1 proteins in streptococcus pneumoniae possess cyclic di-AMP phosphodiesterase activity and affect bacterial growth and virulence. J Bacteriol 195:5123–5132.

Bajaj JS (2019) Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol 16:235–246.

Bajaj JS, Gavis EA, Fagan A, Wade JB, Thacker LR, Fuchs M, Patel S, Davis B, Meador J, Puri P, Sikaroodi M, Gillevet PM (2021) A randomized clinical trial of fecal microbiota transplant for alcohol use disorder. Hepatology 73:1688–1700.

Bjørkhaug ST, Skar V, Medhus AW, Tollisen A, Bramness JG, Valeur J (2017) Chronic alcohol overconsumption may alter gut microbial metabolism: a retrospective study of 719^{13} C-D-xylose breath test results. Microb Ecol Health Dis 28:1301725.

Bjørkhaug ST, Aanes H, Neupane SP, Bramness JG, Malvik S, Henriksen C, Skar V, Medhus AW, Valeur J (2019) Characterization of gut microbiota composition and functions in patients with chronic alcohol overconsumption. Gut Microbes 10:663–675.

Bjørkhaug ST, Neupane SP, Bramness JG, Aanes H, Skar V, Medhus AW, Valeur J (2020) Plasma cytokine levels in

patients with chronic alcohol overconsumption: relations to gut microbiota markers and clinical correlates. Alcohol 85:35–40.

Blagojevic M, Camilli G, Maxson M, Hube B, Moyes DL, Richardson JP, Naglik JR (2021) Candidalysin triggers epithelial cellular stresses that induce necrotic death. Cell Microbiol 23:e13371.

Blednov YA, Benavidez JM, Black M, Harris RA (2014) Inhibition of phosphodiesterase 4 reduces ethanol intake and preference in C57BL/6J mice. Front Neurosci 8:129.

Bluemel S, Wang L, Kuelbs C, Moncera K, Torralba M, Singh H, Fouts DE, Schnabl B (2020) Intestinal and hepatic microbiota changes associated with chronic ethanol administration in mice. Gut Microbes 11:265–275.

Bores-Walmsley MI, Walmsley AR (2000) cAMP signalling in pathogenic fungi: control of dimorphic switching and pathogenicity. Trends Microbiol 8:133–141.

Brown ES, Van Enkevort E, Kulikova A, Escalante C, Nakamura A, Ivleva EI, Holmes T (2019a) A randomized, double-blind, placebo-controlled trial of citicoline in patients with alcohol use disorder. Alcohol Clin Exp Res 43:317–323.

Budden KF, Gellatly SL, Wood DL, Cooper MA, Morrison M, Hugenholtz P, Hansbro PM (2017) Emerging pathogenic links between microbiota and the gut-lung axis. Nat Rev Microbiol 15:55–63.

Burnette EM, Ray LA, Irwin MR, Grodin EN (2021) Ibudilast attenuates alcohol cue-elicited frontostriatal functional connectivity in alcohol use disorder. Alcohol Clin Exp Res 45:2017–2028.

Canesso MCC, Lacerda NL, Ferreira CM, Gonçalves JL, Almeida D, Gamba C, Cassali G, Pedroso SH, Moreira C, Martins FS, Nicoli JR, Teixeira MM, Godard ALB, Vieira AT (2014) Comparing the effects of acute alcohol consumption in germ-free and conventional mice: the role of the gut microbiota. BMC Microbiol 14:240.

Carvalho AF, Heilig M, Perez A, Probst C, Rehm J (2019) Alcohol use disorders. Lancet 394:781–792.

Castrén S, Mäkelä N, Alho H (2019) Selecting an appropriate alcohol pharmacotherapy: review of recent findings. Curr Opin Psychiatry 32:266–274.

Chen P, Miyamoto Y, Mazagova M, Lee KC, Eckmann L, Schnabl B (2015a) Microbiota protects mice against acute alcohol-induced liver injury. Alcohol Clin Exp Res 39:2313–2323.

Chen P, Torralba M, Tan J, Embree M, Zengler K, Stärkel P, van Pijkeren JP, DePew J, Loomba R, Ho SB, Bajaj JS, Mutlu EA, Keshavarzian A, Tsukamoto H, Nelson KE, Fouts DE, Schnabl B (2015b) Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice. Gastroenterology 148:203–214.e16.

Chu H, Duan Y, Lang S, Jiang L, Wang Y, Llorente C, Liu J, Mogavero S, Bosques-Padilla F, Abraldes JG, Vargas V, Tu XM, Yang L, Hou X, Hube B, Stärkel P, Schnabl B (2020) The *Candida albicans* exotoxin candidalysin promotes alcohol-associated liver disease. J Hepatol 72:391–400.

Ciocan D, Rebours V, Voican CS, Wrzosek L, Puchois V, Cassard AM, Perlemuter G (2018) Characterization of intestinal microbiota in alcoholic patients with and without alcoholic hepatitis or chronic alcoholic pancreatitis. Sci Rep 8:4822.

Cohen D, Melamed S, Millman A, Shulman G, Oppenheimer-Shaanan Y, Kacen A, Doron S, Amitai G, Sorek R (2019) Cyclic GMP-AMP signalling protects bacteria against viral infection. Nature 574:691–695.

Coker AR, Weinstein DN, Vega TA, Miller CS, Kayser AS, Mitchell JM (2020) The catechol-O-methyltransferase inhibitor tolcapone modulates alcohol consumption and impulsive choice in alcohol use disorder. Psychopharmacology 237:3139–3148.

Colombo AV, et al. (2021) Microbiota-derived short chain fatty acids modulate microglia and promote Aβ plaque deposition. Elife 10:e59826.

D'Souza CA, Heitman J (2001) Conserved cAMP signaling cascades regulate fungal development and virulence. FEMS Microbiol Rev 25:349–364.

da Silva Furtado Amaral C, da Silva-Boghossian CM, Leão ATT, Colombo APV (2011) Evaluation of the subgingival microbiota of alcoholic and non-alcoholic individuals. J Dent 39:729–738.

Dalile B, Van Oudenhove L, Vervliet B, Verbeke K (2019) The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol 16:461–478.

De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, Backhed F, Mithieux G (2014) Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 156:84–96.

Dickson RP, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, Huffnagle GB (2016) Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol 1:16113.

Drummond RA, Swamydas M, Oikonomou V, Zhai B, Dambuza IM, Schaefer BC, Bohrer AC, Mayer-Barber KD, Lira SA, Iwakura Y, Filler SG, Brown GD, Hube B, Naglik JR, Hohl TM, Lionakis MS (2019) CARD9^{+} microglia promote antifungal immunity via IL-1β- and CXCL1-mediated neutrophil recruitment. Nat Immunol 20:559–570.

Dubinkina VB, et al. (2017) Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease. Microbiome 5:141.

Ezquer F, Quintanilla ME, Moya-Flores F, Morales P, Munita JM, Olivares B, Landskron G, Hermoso MA, Ezquer M, Herrera-Marschitz M, Israel Y (2021) Innate gut microbiota predisposes to high alcohol consumption. Addict Biol 26:e13018.

Falk DE, et al (2019) Gabapentin enacarbil extended-release for alcohol use disorder: a randomized, double-blind, placebo-controlled, multisite trial assessing efficacy and safety. Alcohol Clin Exp Res 43:158–169.

Fan X, Peters BA, Jacobs EJ, Gapstur SM, Purdue MP, Freedman ND, Alekseyenko AV, Wu J, Yang L, Pei Z, Hayes RB, Ahn J (2018) Drinking alcohol is associated with variation in the human oral microbiome in a large study of American adults. Microbiome 6:59.

Fields CT, Chassaing B, Castillo-Ruiz A, Osan R, Gewirtz AT, de Vries GJ (2018) Effects of gut-derived endotoxin on anxiety-like and repetitive behaviors in male and female mice. Biol Sex Differ 9:7.

Foulke-Abel J, Yu H, Sunuwar L, Lin R, Fleckenstein JM, Kaper JB, Donowitz M (2020) Phosphodiesterase 5 (PDE5) restricts intracellular cGMP accumulation during enterotoxigenic *Escherichia coli* infection. Gut Microbes 12:1752125.

Fuchs EL, Brutinel ED, Klem ER, Fehr AR, Yahr TL, Wolfgang MC (2010) In vitro and in vivo characterization of the *Pseudomonas aeruginosa* cyclic AMP (cAMP) phosphodiesterase CpdA, required for cAMP homeostasis and virulence factor regulation. J Bacteriol 192:2779–2790.

Fujisaka S, Avila-Pacheco J, Soto M, Kostic A, Dreyfuss JM, Pan H, Ussar S, Altindis E, Li N, Bry L, Clish CB, Kahn CR (2018) Diet, genetics, and the gut microbiome drive dynamic changes in plasma metabolites. Cell Reports 22:3072–3086.

Gao B, Emami A, Zhou R, Lang SJ, Duan Y, Wang Y, Jiang L, Loomba R, Brenner DA, Stärkel P, Schnabl B (2020) Functional microbial

responses to alcohol abstinence in patients with alcohol use disorder. Front Physiol 11:370.

Gao B, Zhang XL, Schnabl B (2021a) Fungi-bacteria correlation in alcoholic hepatitis patients. Toxins 13:143.

Gao W, Zhu Y, Ye J, Chu H (2021b) Gut non-bacterial microbiota contributing to alcohol-associated liver disease. Gut Microbes 13:1984122.

Garbutt JC, Kampov-Polevoy AB, Pedersen C, Stansbury M, Jordan R, Willing L, Gallop RJ (2021) Efficacy and tolerability of baclofen in a U.S. community population with alcohol use disorder: a dose-response, randomized, controlled trial. Neuropsychopharmacol 46:2250–2256.

Giménez-Gómez P, Pérez-Hernández M, O'Shea E, Caso JR, Martín-Hernandez D, Cervera LA, Gómez-Lus Centelles ML, Gutiérrez-Lopez MD, Colado MI (2019) Changes in brain kynurenine levels via gut microbiota and gut-barrier disruption induced by chronic ethanol exposure in mice. FASEB J 33:12900–12914.

Gobejishvili L, Avila DV, Barker DF, Ghare S, Henderson D, Brock GN, Kirpich IA, Joshi-Barve S, Mokshagundam SPL, McClain CJ, Barve S (2011) S-adenosylmethionine decreases lipopolysaccharide-induced phosphodiesterase 4B2 and attenuates tumor necrosis factor expression via cAMP/protein kinase A pathway. J Pharmacol Exp Ther 337:433–443.

Grodin EN, Bujarski S, Towns B, Burnette E, Nieto S, Lim A, Lin J, Miotto K, Gillis A, Irwin MR, Evans C, Ray LA (2021) Ibudilast, a neuroimmune modulator, reduces heavy drinking and alcohol cue-elicited neural activation: a randomized trial. Transl Psychiatry 11:355.

Gurwara S, Dai A, Ajami NJ, Graham DY, White DL, Chen L, Jang A, Chen E, El-Serag HB, Petrosino JF, Jiao L (2020) Alcohol use alters the colonic mucosa-associated gut microbiota in humans. Nutr Res 83:119–128.

Hamarneh SR, Kim BM, Kaliannan K, Morrison SA, Tantillo TJ, Tao Q, Mohamed MMR, Ramirez JM, Karas A, Liu W, Hu D, Teshager A, Gul SS, Economopoulos KP, Bhan AK, Malo MS, Choi MY, Hodin RA (2017) Intestinal alkaline phosphatase attenuates alcohol-induced hepatosteatosis in mice. Dig Dis Sci 62:2021–2034.

Han SH, Suk KT, Kim DJ, Kim MY, Baik SK, Kim YD, Cheon GJ, Choi DH, Ham YL, Shin DH, Kim EJ (2015) Effects of probiotics (cultured *Lactobacillus subtilis/Streptococcus faecium*) in the treatment of alcoholic hepatitis: randomized-controlled multicenter study. Eur J Gastroenterol Hepatol 27:1300–1306.

Hartmann P, et al (2018) Modulation of the intestinal bile acid/farnesoid X receptor/fibroblast growth factor 15 axis improves alcoholic liver disease in mice. Hepatology 67:2150–2166.

Hartmann P, Lang S, Zeng S, Duan Y, Zhang X, Wang Y, Bondareva M, Kruglov A, Fouts DE, Stärkel P, Schnabl B (2021) Dynamic changes of the fungal microbiome in alcohol use disorder. Front Physiol 12:699253.

Hermann R, Nassr N, Lahu G, Péterfai E, Knoerzer D, Herzog R, Zech K, de Mey C (2007) Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. Clin Pharmacokinet 46:403–416.

Huang G, Huang Q, Wei Y, Wang Y, Du H (2019) Multiple roles and diverse regulation of the Ras/cAMP/protein kinase A pathway in *Candida albicans*. Mol Microbiol 111:6–16.

Human Microbiome Project Consortium. (2012) Structure, function and diversity of the healthy human microbiome. Nature 486:207–214.

Imamura R, Yamanaka K, Ogura T, Hiraga S, Fujita N, Ishihama A, Niki H (1996) Identification of the cpdA gene encoding cyclic 3',5'-adenosine monophosphate phosphodiesterase in *Escherichia coli*. J Biol Chem 271:25423–25429.

Jiang L, et al (2020) Intestinal virome in patients with alcoholic hepatitis. Hepatology 72:2182–2196.

Jung WH, Wam P, Ragni E, Popolo L, Nunn CD, Turner MP, Stateva L (2005) Deletion of PDE2, the gene encoding the high-affinity cAMP phosphodiesterase, results in changes of the cell wall and membrane in *Candida albicans*. Yeast 22:285–294.

Kershaw CD, Guidot DM (2008) Alcoholic lung disease. Alcohol Res Health 31:66–75.

Kim HS, Kim SM, Lee HJ, Park SJ, Lee KH (2009) Expression of the cpdA gene, encoding a 3',5'-cyclic AMP (cAMP) phosphodiesterase, is positively regulated by the cAMP-cAMP receptor protein complex. J Bacteriol 191:922–930.

Kim SS, Eun JW, Cho HJ, Song DS, Kim CW, Kim YS, Lee SW, Kim YK, Yang J, Choi J, Yim HJ, Cheong JY (2021) Microbiome as a potential diagnostic and predictive biomarker in severe alcoholic hepatitis. Aliment Pharmacol Ther 53:540–551.

Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, Maeda T, Terasawa K, Kashihara D, Hirano K, Tani T, Takahashi T, Miyauchi S, Shioi G, Inoue H, Tsujimoto G (2013) The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nat Commun 4:1829.

Kranzler HR, Soyka M (2018) Diagnosis and pharmacotherapy of alcohol use disorder a review. JAMA 320:815–824.

Kumar R, Maulik M, Pathirana RU, Cullen PJ, Edgerton M (2020) Sho1p connects Glycolysis to Ras1-cAMP signaling and is required for microcolony formation in Candida albicans. mSphere 5:e00366–20.

Lakics V, K EH, Boess FG (2010) Quantitative comparison of phosphodiesterase mRNA distribution in human brain and peripheral tissues. Neuropharmacology 59:367–374.

Lamas-Paz A, et al (2020) Intestinal epithelial cell-derived extracellular vesicles modulate hepatic injury via the gut-liver axis during acute alcohol injury. Front Pharmacol 11:603771.

Lang S, et al. (2019) Intestinal fungal dysbiosis and systemic immune response to fungi in patients with alcoholic hepatitis. Hepatology 71:522–538.

Lang S, Fairfied B, Gao B, Duan Y, Zhang XL, Fouts DE, Schnabl B (2020) Changes in the fecal bacterial microbiota associated with disease severity in alcoholic hepatitis patients. Gut Microbes 12:1785251.

Leclercq S, Cani PD, Neyrinck AM, Stärkel P, Jamar F, Mikolajczak M, Delzenne NM, de Timary P (2012) Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects. Brain Behav Immun 26:911–918.

Leclercq S, De Saeger C, Delzenne N, de Timary P, Starkel P (2014b) Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. Biol Psychiatry 76:725–733.

Lee J, d'Aigle J, Atadja L, Quaicoe V, Honarpisheh P, Ganesh BP, Hassan A, Graf J, Petrosino J, Putluri N, Zhu L, Durgan DJ, Bryan RM, McCullough LD, Venna VR (2020) Gut microbiota-derived short-chain fatty acids promote poststroke recovery in aged mice. Circ Res 127:453–465.

Li H, Shi J, Zhao L, Guan J, Liu F, Huo G, Li B (2021) *Lactobacillus plantarum* KLDS1.0344 and *Lactobacillus acidophilus* KLDS1.0901 mixture prevents chronic alcoholic liver injury in mice by protecting the intestinal barrier and regulating gut microbiota and liver-related pathways. J Agric Food Chem 69:183–197.

Li J, Chen D, Yu B, He J, Zheng P, Mao X, Yu J, Luo J, Tian G, Huang Z, Luo Y (2018) Fungi in gastrointestinal tracts of human and mice: from community to functions. Microb Ecol 75:821–829.

Li Y, Shan M, Li S, Wang Y, Yang H, Chen Y, Gu B, Zhu Z (2020) Teasaponin suppresses *Candida albicans* filamentation by reducing the level of intracellular cAMP. Ann Transl Med 8:175.

Llopis M, et al (2016) Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease. Gut 65:830–839.

Logrip ML, Vendruscolo LF, Schlosburg JE, Koob GF, Zorrilla EP (2014) Phosphodiesterase 10A regulates alcohol and saccharin self-administration in rats. Neuropsychopharmacology 39:1722–1731.

Maccioni L, Gao B, Leclercq S, Pirlot B, Horsmans Y, De Timary P, Leclercq I, Fouts D, Schnabl B, Starkel P (2020) Intestinal permeability, microbial translocation, changes in duodenal and fecal microbiota, and their associations with alcoholic liver disease progression in humans. Gut Microbes 12:1782157.

Makitrynskyy R, Tsypik O, Nuzzo D, Paululat T, Zechel DL, Bechthold A (2020) Secondary nucleotide messenger c-di-GMP exerts a global control on natural product biosynthesis in streptomycetes. Nucleic Acids Res 48:1583–1598.

Malhotra N, Chakraborti PK (2016) Eukaryotic-type Ser/Thr protein kinase mediated phosphorylation of mycobacterial phosphodiesterase affects its localization to the cell wall. Front Microbiol 7:123.

Mariani JJ, Pavlicova M, Basaraba C, Mamczur-Fuller A, Brooks DJ, Bisaga A, Carpenter KM, Nunes EV, Levin FR (2021) Pilot randomized placebo-controlled clinical trial of high-dose gabapentin for alcohol use disorder. Alcohol Clin Exp Res 45:1639–1652.

Matange N (2015) Revisiting bacterial cyclic nucleotide phosphodiesterases: cyclic AMP hydrolysis and beyond. FEMS Microbiol Lett 362:fnv183.

McDonough KA, Rodriguez A (2012) The myriad roles of cyclic AMP in microbial pathogens: from signal to sword. Nat Rev Microbiol 10:27–38.

Mizuta K, Sasaki H, Zhang Y, Matoba A, Emala CW Sr (2020) The short-chain free fatty acid receptor FFAR3 is expressed and potentiates contraction in human airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 318:L1248–L1260.

Moss M, Burnham EL (2003) Chronic alcohol abuse, acute respiratory distress syndrome, and multiple organ dysfunction. Crit Care Med 31(4 suppl):S207–S212.

Mutlu EA, Gillevet PM, Rangwala H, Sikaroodi M, Naqvi A, Engen PA, Kwasny M, Lau CK, Keshavarzian A (2012) Colonic microbiome is altered in alcoholism. Am J Physiol Gastrointest Liver Physiol 302:G966–G978.

Myers SA, Gobejishvili L, Ohri SS, Wilson CG, Andres KR, Riegler AS, Donde H, Joshi-Barve S, Barve S, Whittemore SR (2019) Following spinal cord injury, PDE4B drives an acute, local inflammatory response and a chronic, systemic response exacerbated by gut dysbiosis and endotoxemia. Neurobiol Dis 124:353–363.

Palpacuer C, Duprez R, Huneau A, Locher C, Boussageon R, Laviolle B, Naudet F (2018) Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. Addiction 113:220–237.

Panpetch W, Kullapanich C, Dang CP, Visitchanakun P, Saisorn W, Wongphoom J, Wannigama DL, Thim-Uam A, Patarakul K, Somboonna N, Tumwasorn S, Leelahavanichkul A (2021) *Candida* administration worsens uremia-induced gut leakage in bilateral nephrectomy mice, an impact of gut fungi and organismal molecules in uremia. mSystems 6:e01187–20.

Perez-Torres S, Miro X, Palacios JM, Cortes R, Puigdomenech P, Mengod G (2000) Phosphodiesterase type 4 isozymes expression in human brain examined by in situ hybridization histochemistry and [H-3]rolipram binding autoradiography. Comparison with monkey and rat brain. J Chem Neuroanat 20:349–374.

Peterson VL, Jury NJ, Cabrera-Rubio R, Draper LA, Crispie F, Cotter PD, Dinan TG, Holmes A, Cryan JF (2017) Drunk bugs: chronic vapour alcohol exposure induces marked changes in the gut microbiome in mice. Behav Brain Res 323: 172–176.

Podobnik M, Tyagi R, Matange N, Dermol U, Gupta AK, Mattoo R, Seshadri K, Visweswariah SS (2009) A mycobacterial cyclic AMP phosphodiesterase that moonlights as a modifier of cell wall permeability. J Biol Chem 284:32846–32857.

Posteraro B, Sterbini FP, Petito V, Rocca S, Cubeddu T, Graziani C, Arena V, Vassallo GA, Mosoni C, Lopetuso L, Lorrai I, Maccioni P, Masucci L, Martini C, Gasbarrini A, Sanguinetti M, Colombo G, Addolorato G (2018) Liver injury, endotoxemia, and their relationship to intestinal microbiota composition in alcohol-preferring rats. Alcohol Clin Exp Res 42:2313–2325.

Puri P, Liangpunsakul S, Christensen JE, Shah VH, Kamath PS, Gores GJ, Walker S, Comerford M, Katz B, Borst A, Yu QG, Kumar DP, Mirshahi F, Radaeva S, Chalasani NP, Crabb DW, Sanyal AJ; TREAT Consortium (2018) The circulating microbiome signature and inferred functional metagenomics in alcoholic hepatitis. Hepatology 67:1284–1302.

Rao W, Lin Z, Liu S, Zhang Z, Xie Q, Chen H, Lin X, Chen Y, Yang H, Yu K, Hu Z (2021) Association between alcohol consumption and oesophageal microbiota in oesophageal squamous cell carcinoma. BMC Microbiol 21:73–73.

Ray LA, Bujarski S, Shoptaw S, Roche DJ, Heinzerling K, Miotto K (2017) Development of the neuroimmune modulator ibudilast for the treatment of alcoholism: a randomized, placebo-controlled, human laboratory trial. Neuropsychopharmacology 42:1776–1788.

Reyes-Irisarri E, Markerink-Van Ittersum M, Mengod G, de Vente J (2007) Expression of the cGMP-specific phosphodiesterases 2 and 9 in normal and Alzheimer's disease human brains. Eur J Neurosci 25:3332–3338.

Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, Wijsenbeek MS, Zoz DF, Voss F, Maher TM (2022) Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. N Engl J Med 386:2178–2187.

Rodriguez-Rabassa M, Lopez P, Sanchez R, Hernandez C, Rodriguez C, Rodriguez-Santiago RE, Orengo JC, Green V, Yamamura Y, Rivera-Amill V (2020) Inflammatory biomarkers, microbiome, depression, and executive dysfunction in alcohol users. Int J Environ Res Public Health 17:689.

Samuelson DR, Shellito JE, Maffei VJ, Tague ED, Campagna SR, Blanchard EE, Luo M, Taylor CM, Ronis MJJ, Molina PEX, Welsh DA (2017) Alcohol-associated intestinal dysbiosis impairs pulmonary host defense against Klebsiella pneumoniae. PLoS Pathog 13:e1006426.

Samuelson DR, Burnham EL, Maffei VJ, Vandivier RW, Blanchard EE, Shellito JE, Luo M, Taylor CM, Welsh DA (2018) The respiratory tract microbial biogeography in alcohol use disorder. Am J Physiol Lung Cell Mol Physiol 314:L107–L117.

Satoh T, Morisaki H, Ai K, Kosugi S, Yamamoto M, Serita R, Kotake Y, Takeda J (2003) Olprinone, a phosphodiesterase III inhibitor, reduces gut mucosal injury and portal endotoxin level during acute hypoxia in rabbits. Anesthesiology 98:1407–1414.

She X, Zhang L, Peng J, Zhang J, Li H, Zhang P, Calderone R, Liu W, Li D (2020) Mitochondrial complex I core protein regulates

cAMP signaling via phosphodiesterase Pde2 and NAD homeostasis in *Candida albicans*. Front Microbiol 11:559975.

Shi J, Liu H, Pan J, Chen J, Zhang N, Liu K, Fei N, O'Donnell JM, Zhang HT, Xu Y (2018) Inhibition of phosphodiesterase 2 by Bay 60-7550 decreases ethanol intake and preference in mice. Psychopharmacology (Berl) 235:2377–2385.

Shimizu C, Oki Y, Mitani Y, Tsuchiya Y, Nabeshima T (2016) Moderate-dose regular lifelong alcohol intake changes the intestinal flora, protects against aging, and keeps spatial memory in the senescence-accelerated mouse prone 8 (SAMP8) model. J Pharm Sci 19:430–447.

Silva YP, Bernardi A, Frozza RL (2020) The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol (Lausanne) 11:25.

Spatz M, Ciocan D, Merlen G, Rainteau D, Humbert L, Gomes-Rochette N, Hugot C, Trainel N, Mercier-Nomé F, Domenichini S, Puchois V, Wrzosek L, Ferrere G, Tordjmann T, Perlemuter G, Cassard AM (2021) Bile acid-receptor TGR5 deficiency worsens liver injury in alcohol-fed mice by inducing intestinal microbiota dysbiosis. JHEP Rep 3:100230.

Sun S, Wang K, Sun L, Cheng B, Qiao S, Dai H, Shi W, Ma J, Liu H (2020) Therapeutic manipulation of gut microbiota by polysaccharides of *Wolfiporia cocos* reveals the contribution of the gut fungi-induced PGE(2) to alcoholic hepatic steatosis. Gut Microbes 12:1830693.

Thomson M, Liu Y, Nunta K, Cheyne A, Fernandes N, Williams R, Garza-Garcia A, Larrouy-Maumus G (2022) Expression of a novel mycobacterial phosphodiesterase successfully lowers cAMP levels resulting in reduced tolerance to cell wall-targeting antimicrobials. J Biol Chem 298:102151.

Tian X, Li R, Jiang Y, Zhao F, Yu Z, Wang Y, Dong Z, Liu P, Li X (2020) *Bifidobacterium breve* ATCC15700 pretreatment prevents alcoholic liver disease through modulating gut microbiota in mice exposed to chronic alcohol intake. J Funct Foods 72:104045.

van de Wouw M, Boehme M, Lyte JM, Wiley N, Strain C, O'Sullivan O, Clarke G, Stanton C, Dinan TG, Cryan JF (2018) Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J Physiol 596:4923–4944.

Wang A, Si H, Liu D, Jiang H (2012a) Butyrate activates the cAMP-protein kinase A-cAMP response element-binding protein signaling pathway in Caco-2 cells. J Nutr 142:1–6.

Wang G, Liu Q, Guo L, Zeng H, Ding C, Zhang W, Xu D, Wang X, Qiu J, Dong Q, Fan Z, Zhang Q, Pan J (2018) Gut microbiota and relevant metabolites analysis in alcohol dependent mice. Front Microbiol 9:1874.

Wang Y, Liu Y, Sidhu A, Ma Z, McClain C, Feng W (2012b) *Lactobacillus rhamnosus* GG culture supernatant ameliorates acute alcohol-induced intestinal permeability and liver injury. Am J Physiol Gastrointest Liver Physiol 303:G32–G41.

Wen RT, Zhang FF, Zhang HT (2018) Cyclic nucleotide phosphodiesterases: potential therapeutic targets for alcohol use disorder. Psychopharmacology 235:1793–1805.

Wilson D, Tutulan-Cunita A, Jung W, Hauser NC, Hernandez R, Williamson T, Piekarska K, Rupp S, Young T, Stateva L (2007) Deletion of the high-affinity cAMP phosphodiesterase encoded by PDE2 affects stress responses and virulence in *Candida albicans*. Mol Microbiol 65:841–856.

Wilson D, Fiori A, De Brucker K, Van Dijck P, Stateva L (2010) *Candida albicans* Pde1p and Gpa2p comprise a regulatory module mediating agonist-induced cAMP signalling and environmental adaptation. Fungal Genet Biol 47:742–752.

Witkiewitz K, Litten RZ, Leggio L (2019) Advances in the science and treatment of alcohol use disorder. Sci Adv 5:eaax4043.

Wu J, Wu D, Ma K, Wang T, Shi G, Shao J, Wang C, Yan G (2020) Paeonol ameliorates murine alcohol liver disease via mycobiota-mediated Dectin-1/IL-1β signaling pathway. J Leukoc Biol 108:199–214.

Xiao H, Ge C, Feng GX, Li Y, Luo D, Dong JL, Li H, Wang H, Cui M, Fan SJ (2018) Gut microbiota modulates alcohol withdrawal-induced anxiety in mice. Toxicol Lett 287:23–30.

Xie G, Zhong W, Zheng X, Li Q, Qiu Y, Li H, Chen H, Zhou Z, Jia W (2013) Chronic ethanol consumption alters mammalian gastrointestinal content metabolites. J Proteome Res 12:3297–3306.

Xu Z, Liu Z, Dong X, Hu T, Wang L, Li J, Liu X, Sun J (2018) Fecal microbiota transplantation from healthy donors reduced alcohol-induced anxiety and depression in an animal model of chronic alcohol exposure. Chin J Physiol 61:360–371.

Xu Z, Wang C, Dong X, Hu T, Wang L, Zhao W, Zhu S, Li G, Hu Y, Gao Q, Wan J, Liu Z, Sun J (2019) Chronic alcohol exposure induced gut microbiota dysbiosis and its correlations with neuropsychic behaviors and brain BDNF/Gabra1 changes in mice. Biofactors 45:187–199.

Yang AM, et al (2017) Intestinal fungi contribute to development of alcoholic liver disease. J Clin Investig 127:2829–2841.

Yang F, Zhao YE, Wei JD, Lu YF, Zhang Y, Sun YL, Ma MY, Zhang RL (2018) Comparison of microbial diversity and composition in the jejunum and colon of alcohol-dependent rats. J Microbiol Biotechnol 28:1883–1895.

Yu L, Wang L, Yi HX, Wu XJ (2020) Beneficial effects of LRP6-CRISPR on prevention of alcohol-related liver injury surpassed fecal microbiota transplant in a rat model. Gut Microbes 11:1015–1029.

Yue R, Wei X, Zhao J, Zhou Z, Zhong W (2021) Essential role of IFN-gamma in regulating gut antimicrobial peptides and microbiota to protect against alcohol-induced bacterial translocation and hepatic inflammation in mice. Front Physiol 11:629141.

Zhao W, Hu Y, Li C, Li N, Zhu S, Tan X, Li M, Zhang Y, Xu Z, Ding Z, Hu L, Liu Z, Sun J (2020) Transplantation of fecal microbiota from patients with alcoholism induces anxiety/depression behaviors and decreases brain mGluR1/PKC epsilon levels in mouse. Biofactors 46:38–54.

Zhou F, Wang X, Han B, Tang X, Liu R, Ji Q, Zhou Z, Zhang L (2021) Short-chain fatty acids contribute to neuropathic pain via regulating microglia activation and polarization. Mol Pain 17:1744806921996520.