# Microbiota-derived psychedelics: Lessons from COVID-19

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## Abstract

Emil Kraepelin believed that dementia praecox, the disorder we now call schizophrenia, was caused by the brain being poisoned with toxins generated in other parts of the body, especially the mouth, intestine or genitals. In this regard, Kraepelin hinted at the microbiome and conceptualized microbial molecules as drivers of severe psychiatric illness. However, it was not until the coronavirus disease (COVID-19) pandemic that Kraepelin's paradigm gained traction, particularly because this virus was associated with both gut barrier disruption and new-onset psychosis.

Likewise, despite numerous studies linking severe psychiatric illness to genomic damage and dysfunctional DNA repair, this pathogenetic mechanism was underappreciated before the COVID-19 pandemic.

The use of the psychotomimetic anesthetic, ketamine, for treatment-resistant depression has reawakened the interest in endogenous serotonergic hallucinogens, especially tryptamine and N,N-dimethyltryptamine (DMT), which are beneficial for depression but associated with psychosis.

In this editorial, we take a closer look at the role of the microbiome in psychopathology, attempting to answer 2 questions:

1. Why may psychosis-predisposing serotonergic hallucinogens alleviate depression?
2. Are microbiota-derived psychedelics part of an inbuilt antidepressant system similar to endogenous opioids?

**Key words:** gut microbes, serotonergic hallucinogens, severe psychiatric illness

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## Introduction

Two major advances, the discovery of trace amine-associated receptors (TAARs) in 2001 and ketamine use for treatment-resistant depression, have contributed to a better understanding of the gut microbiota's role in psychopathology.[1,2]

These findings were further corroborated by the discovery, in 2014, of tryptophan decarboxylase-expressing gut commensals capable of converting dietary tryptophan into tryptamine, a serotonergic hallucinogen previously implicated in schizophrenia.[3–5] Although the physiological role of endogenous hallucinogens so far unknown, translocation of tryptophan decarboxylase-expressing microbes into the host systemic circulation may enable tryptamine to access the central nervous system (CNS) and interact with brain TAARs.[6] Indeed, the discovery of N,N-dimethyltryptamine (DMT) and N-acetyltryptamine (NAT) in rat pineal gland suggests that endogenous hallucinogens are either synthesized in the CNS or derived from gut microbes.[7,8]

We hypothesize that serotonergic hallucinogens and their CNS receptors comprise an endogenous antidepressant system mediated by TAARs, and that elevated levels of tryptamine or DMT due to a disrupted gut barrier may activate 5-hydroxytryptamine 2A receptors (5HT2ARs) and the aryl hydrocarbon receptor (AhR), and in consequence trigger psychosis. In other words, the activation of TAAR may drive the antidepressant effect, while stimulation of 5HT2ARs and AhR may engender psychosis.

## Loose microbes and aberrant microglia

Studies on intestinal barrier disruption and an increased prevalence of psychiatric disorders after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have contributed to a better understanding of the physiological role of microbiota-generated serotonergic hallucinogens as well as the participation of other gut microorganisms in the pathogenesis of severe psychiatric illness (SPI), conceptualized as mental or behavioral conditions which substantially interfere with patients' life activities.[9–16]

Along this line, a recent retrospective study found that 19.5% of coronavirus disease (COVID-19) survivors developed depression or anxiety, and nearly 2.8% developed new-onset psychosis, linking the SARS-CoV-2 disruption of the gut barrier to neuropathology.[17] The psychological stress caused by contracting COVID-19, a potentially fatal disease, as well as the subsequent restrictive measures, including mandatory isolation and social distancing, can trigger mood and anxiety disorders. However, psychological stress has been associated with the impairment of both the gut barrier and microglial activation.[18–20] Indeed, several viral infections, including COVID-19 and human immunodeficiency virus (HIV), were associated with higher rates of post-traumatic stress disorder (PTSD) than those found in war veterans as well as military and law enforcement personnel, suggesting that aside from psychosocial stress, viruses could directly interfere with the gut and/or blood–brain barrier (BBB).[21–23] Moreover, microbial translocation markers, including zonulin, intestinal fatty acid binding protein (I-FABP) and soluble CD14 (sCD14), were documented in people with depression and suicidal behavior.[24] Along this line, a novel study linked suicidal ideation with depletion of the oral microbe *Alloprevotella rava* spp., further emphasizing the role of microbiota in neuropathology.[25] Indeed, previous studies have associated SPI with increased gastrointestinal (GI) tract permeability measured by the levels of microbial translocation markers.[26,27] In this regard, earlier data linked SPI

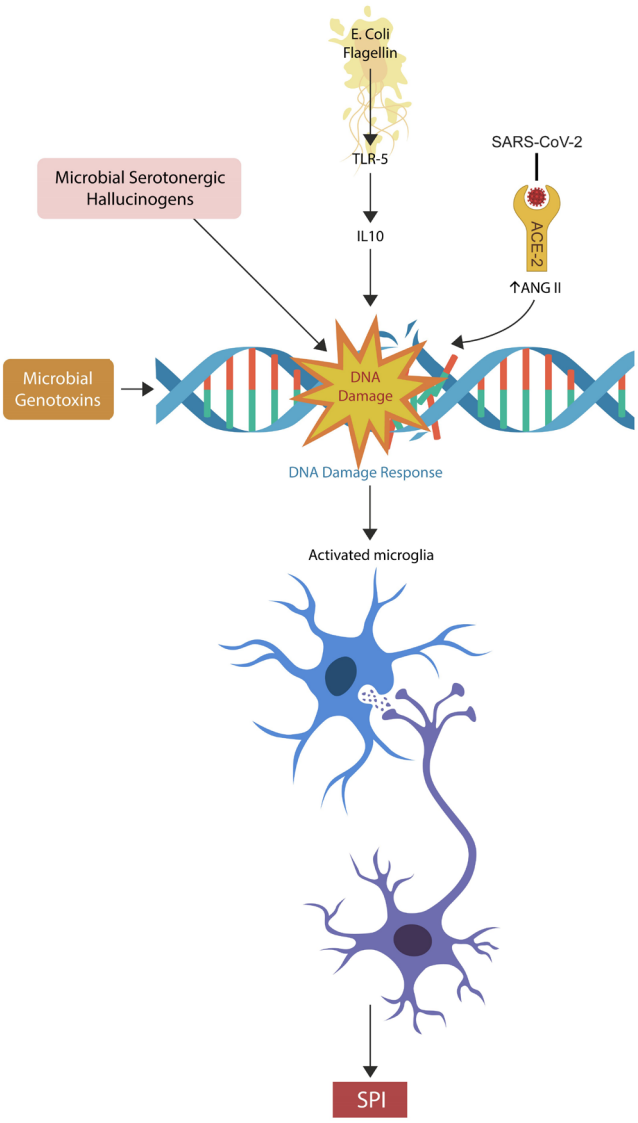


Fig. 1. Numerous pathogens and their molecules can damage the host genome. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus upregulates angiotensin II (ANG II), a genotoxin, by inhibiting its hydrolyzing enzyme, ACE-2. The *Escherichia coli* spp. (*E. coli*) protein, flagellin, activates toll-like receptor-5 (TLR-5), upregulating interleukin 10 (IL-10) that in turn can damage the DNA. Dysfunctional serotonergic hallucinogens and bacterial genotoxins can inflict additional genomic damage, activate microglia and cause severe psychiatric illness (SPI) by aberrant phagocytosis of viable neurons

to the translocation of *Escherichia coli* spp. (*E. coli*) into the host systemic circulation.[28,29] In addition, neuropsychiatric symptoms, including psychosis, were documented in 2011 during an *E. coli* outbreak in northern Germany, further connecting this bacterium to neuropathology.[30,31] Moreover, *E. coli* antigens, including lipopolysaccharide (LPS) and flagellin, were shown to aberrantly activate microglia, potentially leading to pathological phagocytosis of viable neurons and/or synapses.[32,33] Flagellin, a Toll-like receptor-5 (TLR-5) agonist, was demonstrated to activate neurotoxic microglia, inducing gray matter loss in patients with SPI[34,35] (see the section on microbial genotoxins and SPI). Interestingly, serotonergic hallucinogen DMT was found capable of protecting neurons by deactivating microglia, emphasizing an important physiological function of this biomolecule.[36]

Taken together, these studies show that the systemic translocation of bacteria and/or their molecules can activate neurotoxic microglia that aberrantly eliminate healthy neurons. On the other hand, serotonergic hallucinogens may show neuroprotective properties by inhibiting neurotoxic microglia.

## Endogenous hallucinogens – friends or foes?

Early studies, in the 1960s and 1970s, have connected SPI with endogenous hallucinogens derived from several sources, including the microbial metabolism of tryptophan.[3,4] These older studies were disregarded at the time due to the levels of endogenous psychedelics being considered too low to produce significant biological effects. However, the discovery of TAARs capable of sensing nanomolar ligand quantities has reawakened the interest in endogenous hallucinogens and their involvement in SPI.[37,38] As both ketamine, an N-methyl-D-aspartate (NMDA) receptor blocker, and serotonergic hallucinogens exhibit fast-acting antidepressant effects, it begs the question: how can psychosis-associated molecules alleviate depression?[39]

We surmise that microbiota-derived serotonergic hallucinogens are beneficial for severe depression as they induce limited genomic disruption that activates DNA damage repair (DDR), a neuroplasticity-mediating physiological process. Indeed, novel studies have shown that DDR comprises an adaptive mechanism that enhances neuronal plasticity and long-term potentiation.[40,41] On the other hand, irreparable genomic damage, leading to neuronal death, contributes to the pathogenesis of neurodegenerative disorders and/or psychosis.[42,43] For example, recreational use of exogenous hallucinogens may inflict extensive DNA damage, triggering psychosis, a pathology documented in users of d-lysergic acid diethylamide (LSD) or psilocybin.[44,45]

Taken together, limited DNA damage enhances neuroplasticity, inducing antidepressant effects. On the other hand, extensive genomic damage may trigger psychosis or neurodegeneration by converting microglia into a neurotoxic phenotype.

## Microbial genotoxins and SPI

The SARS-CoV-2 virus was found to disrupt the human genome, probably accounting for the new-onset psychosis that sometimes accompanies COVID-19 critical illness.[46,47] Indeed, DNA damage-induced neuropathology, though a phenomenon already known before the COVID-19 pandemic, remained underappreciated as a pathogenetic factor of SPI until recently.[48–53]

Several *E. coli* species were demonstrated to produce colibactin, a genotoxic molecule associated with inflammatory bowel disease (IBD), colorectal carcinoma (CRC) and possibly schizophrenia. Moreover, *Morganella morganii* spp. (*M. morganii*) was found to damage the host DNA by releasing indolimines, genotoxic colibactin-like molecules.[54] Interestingly, both *E. coli* and *M. morganii* were previously implicated in schizophrenia, further linking DNA damage to psychopathology.[55] Interestingly, *M. morganii* was demonstrated to cause food poisoning by secreting serotonergic hallucinogens and histamine, connecting this gut commensal to SPI.[56–58]

Aside from damaging the DNA, both colibactin and indolimine can increase the permeability of the gut barrier, facilitating microbial translocation from the GI tract into host tissues.[59–63] In addition, colibactin and indolimine were demonstrated to activate bacteriophages in gut microbes, likely increasing the abundance of bacteriophage-resistant tryptophan decarboxylase-expressing commensals and the levels of endogenous hallucinogens.[64,65] Notably, patients with schizophrenia were recently reported to exhibit altered oropharyngeal bacteriophages (phageome), connecting this disorder to microbial genotoxin-induced DNA damage.[66] Several studies connected interleukin 10 (IL-10) with *E. coli* infection, a microbe associated with genomic damage and schizophrenia (Fig. 1).[67]

Taken together, some gut microbes release genotoxic molecules that can reactivate both latent viruses, such as Epstein–Barr virus (EBV), as well as bacteriophages, triggering various pathologies, including SPI.[68]

## The link between the microbiome and SPI

Several studies have reported altered microbial composition in patients with SPI.[69] For example, compared to healthy controls, the fecal microbiome of patients with schizophrenia exhibits an increased abundance of phylum Proteobacteria, especially genus *Succinivibrio*.[70] On the other hand, the oropharyngeal microbiome of individuals with first-episode psychosis (FEP) was found to display increased levels of lactic acid bacteria and *Lactobacillus* phage.[66,71] As lactic acid microbes utilize glucose as a carbon source for generating pyruvate, these changes in the microbiome likely point to the preponderance of glycolysis as compared to oxidative phosphorylation

(OXPHOS) in SPI.[72] Indeed, mitochondrial dysfunction and impaired OXPHOS were previously demonstrated in schizophrenia.[73]

## Conclusions

Gut microbiota, comprised of bacteria, fungi and viruses, can underlie pathological circumstances and translocate outside the GI tract, triggering immunogenicity and hyperinflammation that may disrupt both the host genome and DDR, engendering SPI.

Gut microbiota-generated endogenous hallucinogens, acting via TAARs, likely comprise an inbuilt antidepressant system akin to endogenous opioids. Dysfunctional AhR signaling can damage neuronal DNA, inducing SPI by neurotoxic microglia.

More studies are needed to elucidate the antidepressant function as well as the nonmicrobial sources of endogenous hallucinogens, as it is currently uncertain whether these compounds are also synthesized in the human brain.

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