

Review

Gut Microbiota and Antipsychotics Induced Metabolic Alteration

Dong-Yu Kang¹, Su-Juan Li¹, Chen-Chen Liu¹, Ren-Rong Wu^{1,2*}

¹Mental Health Institute of the Second Xiangya Hospital, Central South University; Chinese National Clinical Research Center on Mental Disorders; Chinese National Technology Institute on Mental Disorders; Hunan Key Laboratory of Psychiatry and Mental Health, Changsha, Hunan 410011, China; ²Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

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ABSTRACT

Schizophrenia is a chronic and severe mental disorder with antipsychotics as primary medications, but the antipsychotics-induced metabolic side effects may contribute to the elevated risk of overall morbidity and mortality in patients with psychiatric diseases. With the development in sequencing technology and bioinformatics, dysbiosis has been shown to contribute to body weight gain and metabolic dysfunction. However, the role of gut microbiota in the antipsychotics-induced metabolic alteration remains unknown. In this paper, we reviewed the recent studies of the gut microbiota with psychiatric disorders and antipsychotic-induced metabolic dysfunction. Patients with neuropsychiatric disorders may have a different composition of gut microbiota compared with healthy controls. In addition, it seems that the use of antipsychotics is concurrently associated with both altered composition of gut microbiota and metabolic disturbance. Further study is needed to address the role of gut microbiota in the development of neuropsychiatric disorders and antipsychotic-induced metabolic disturbance, to develop novel therapeutics for both neuropsychiatric disorders and metabolic dysfunction.

KEYWORDS:

Gut microbiota, Neuropsychiatric disorder, Metabolism, Antipsychotics

INTRODUCTION

Since microbes have existed hundreds of millions to billions of years, multicellular animals including humans arose in a microbiologically complex environment. However, not until recent decades have we started to appreciate the fact that we harbor at least 100 trillion microbial cells (1), far more than the number of human cells in the body. The microbes that reside in and on the human body all together constitute our microbiota and the collection of genes they encode are named as the microbiome (2). The human gut microbiota is dominated by two bacterial phyla, *Bacteroidetes* and *Firmicutes* (3). Though many factors could affect microbial composition in the human gut, it is surprisingly stable at the phylum level (4). However, when the compositions of genera and species were considered, the inter-individual variation was relatively higher (5).

Along with the development in sequencing technology and bioinformatics, the more in-depth investigations into the composition and the role of complex microbial ecosystems

in neuroscience have become possible in the recent decade (6). Current researches hypothesize that the gut microbiota interacts with the host through immune, neuroendocrine and neural pathways (7), and gut microbiota can modify the synthesis of key metabolites that affect the gene expression in the prefrontal cortex and then modulate social behaviors (8). The microbiota-gut-brain communication might modulate brain development, function and even behaviors, and therefore therapeutics target at the microbiota-gut-brain could provide effective treatment for psychiatric disorders.

Antipsychotics are widely used to treat schizophrenia and bipolar disorder, but some of these drugs commonly cause metabolic side-effects, including the increased incidence of obesity, diabetes, and metabolic dysfunction, which contribute to the risk of overall morbidity and mortality (9). Accumulating evidence shows an increased prevalence of obesity and metabolic dysfunction such as impaired fasting glucose and insulin resistance in drug-naïve first-episode

* Correspondence to: RR Wu, Email: wurenrong@csu.edu.cn

patients with schizophrenia, suggesting a possible co-morbidity of metabolic dysfunction in patients with schizophrenia (10). Metabolic complications such as weight gain could be distressing(11) and has become a significant concern in selecting medications for individuals with psychotic diseases for it is often associated with a poorer functional outcome(12), reduced quality of life(13), and likelihood of discontinuing antipsychotic medications (14). The mechanism of antipsychotic-induced metabolic dysfunction remains unknown. Despite that, previous studies have indicated some possible pathways that might contribute to antipsychotic-induced metabolic dysfunction.

The use of antipsychotics can significantly increase appetite (15). The central and peripheral mechanism for regulating hunger and satiety plays a vital role in the maintenance of energy homeostasis, which involves gut hormones such as glucagon-like peptide 1(GLP-1), peptide YY (PYY), and ghrelin, and adipokines such as leptin (16) and adiponectin (17). Gut hormones are a group of hormones secreted by enteroendocrine cells in the stomach, pancreas, and small intestine that control various functions of the digestive organs. For example, GLP-1 increases insulin secretion; PYY inhibits food intake; ghrelin stimulates appetite and increases gastric emptying. Adipokines are cytokines secreted by adipose tissue (18). As adipokines, leptin helps regulate energy balance by inhibiting hunger, which in turn reduced fat storage in adiposities, while adiponectin is involved in regulating the levels of glucose and fatty acid breakdown. Those peripheral signals were integrated into the arcuate nucleus of the hypothalamus, which contains orexigenic neuropeptide Y (NPY) neurons and anorexigenic pro-opiomelanocortin (POMC) (19).

The antipsychotic medications may decrease the resting energy expenditure in youth (20) and adults (21). Resting energy expenditure or fat-free mass ratio is significantly increased and correlated with the weight gain during the follow-up of adolescents who took antipsychotics (22). However, after adjusting the energy expenditure for fat-free mass, there is no significant difference for individuals with schizophrenia and healthy controls, suggesting that the different body composition and impaired capacity to use fat to generate energy may play a vital role in developing weight gain (23). Besides, many studies have shown that antipsychotic medications could induce a significant risk of insulin resistance, glucose dysregulation, and the development of type 2 diabetes (9). Individuals with psychiatric disorders like drug-naive first-episode schizophrenia are reported to have an elevated risk for diabetes before using antipsychotics, suggesting a possible common underlying schizophrenia and metabolic dysfunction (24).

A recent study by Maier et al. suggests that almost one-quarter of non-antibiotic drugs used in humans, mainly antipsychotics, have antimicrobial activity, which may cause an imbalance to the gut microbiota ecosystem (25). Meanwhile, dysbiosis may contribute to bodyweight alterations and metabolic dysfunction (26). This may provide a new avenue for understanding the mechanism of antipsychotic-induced metabolic disturbance. Therefore, we prepared this review to summarize recent findings in both clinical trials

and animal studies linking gut microbiota, psychotic disorders, and antipsychotic-induced metabolic alterations.

GUT MICROBIOTA AND PSYCHIATRY DISORDERS

Altered composition of gut microbiota has been found in patients with schizophrenia (27), autism spectrum disorder (ASD) (28), bipolar disorder (29), and major depressive disorder (30), which have been considered major mental health disorders (31), with a peak age of onset in children, adolescents and younger adults. Emerging research indicates implicated that the gut microbiota plays a crucial role in the development of the nervous system, neuropsychiatric disorders, and drug response (32). However, the pathophysiological link with brain disorders has yet to be established. There are several bidirectional pathways through which the gut microbiota might affect the brain function(28), which may be the potential underlying mechanism of several neuropsychiatric disorders.

Microbiota-gut-brain-axis: communication between gut and brain

One critical pathway is the communication between the gut microbiome and the host immune system (33). The gut microbiota might trigger the production of various immune-related cytokines that could media signaling pathway (34) and is also related to the pathogenesis of inflammatory bowel disease (IBD) (35). Meanwhile, gut microbiota could communicate with the nervous system through production of neurotransmitters (Figure 1). For example, gut microbiota such as *Lactobacillus(L.) brevis* and *Bifidobacterium(B.) dentium* have been reported to produce gamma-aminobutyric acid (GABA) that might affect GABAergic neurotransmission (36), and another group of neurotransmitters such as norepinephrine, and dopamine, which has been linked to schizophrenia(37). Also, *L. reuteri* could produce histamines, which are linked to major depression and cognitive function (38).

Gut microbiota could directly communicate to the central nervous system to maintain a sense of homeostasis in the physiological condition through the vagus nerve in the human body (39). The beneficial effects of *L. rhamnosus* chronic treatment were not found in vagotomized mice, which may indicate the vagus as a significant modulatory pathway between gut microbiota and the brain (40). The endocrine signaling pathway may be also involved in the communication between brain and gut microbiota. Previous research reported that prebiotic treatment significantly changed the composition of gut microbiota in healthy adults, and increased the plasma concentrations of GLP-1 and PYY, which participated in appetite and glucose excursion responses after meal (41). Another focus of recent studies is that the gut microbiota metabolized short-chain fatty acids (SCFAs). Sun et al. reported that microbiota regulated Th1 cell functions to maintain intestinal homeostasis through gut microbiota-derived SCFAs (42). SCFAs produced by gut microbiota also links metabolic activity of the gut microbiota with host body energy homeostasis and inhibit fat accumulation in adipose tissue (43).

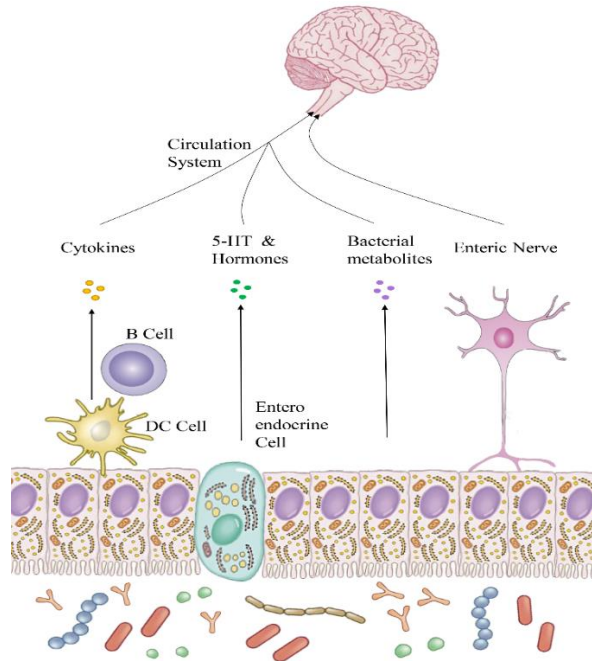


Figure 1. The various known bidirectional-signaling pathways between the gut microbiota and the brain, including immune, neuroendocrine and neural pathways. DC cell, dendritic cell; 5-HT, 5-hydroxytryptamine.

Schizophrenia

The increased morbidity of IBD and gastroenterology issues have been noted with psychiatric disorders and schizophrenia (44, 45). This association suggests that there is a plausible basis for hypothesizing that schizophrenia and microbiota have a functional relationship. Recently, more studies have been focusing on the link between schizophrenia and microbiome (46, 47). For instance, the higher rate of IBD may be related to the immune origins of schizophrenia (48). One preliminary study found an altered composition of microbiota in patients with first-episode schizophrenia compared with age-matched healthy controls.

Meanwhile, reduced numbers of *Lactobacillus* and *Bifidobacterium* species may be correlated with the severity of negative symptoms and less likelihood of remission at 12-month follow-up in individuals with first-episode schizophrenia (49). One recent mega-genomic study of 90 drug-free patients with schizophrenia identified 26 schizophrenia-associated bacterial species, in which the discovered genes are enriched in SCFA synthesis, tryptophan metabolism, and synthesis/degradation of several neurotransmitters (50). Germ-free mice given fecal transplants from schizophrenia patients tend to have lower glutamate and higher glutamine and GABA in the hippocampus and display schizophrenia-relevant behaviors (51). However, probiotic supplements had no effects on psychopathological symptoms measured by positive and negative symptom scales (PANSS) in individuals with schizophrenia, though the treatment reduced severe bowel symptoms associated with antipsychotics (52). In addition, one recent systematic review also suggests that based on the current evidence,

there are no significant differences in psychopathological symptoms between the group of patients with schizophrenia given either probiotic supplements and placebo (53).

Bipolar disorder

Yolken et al. reported that individuals hospitalized with acute mania have a significantly increased rate of bacterial infections (54). The hypothesis that gut microbiota related immune activation may contribute to the onset of bipolar disorder has since emerged (55). The difference in gut microbial composition has been associated with bipolar disorder and self-reported burden of diseases. *Faecalibacterium* and an unclassified member of the *Ruminococcaceae* family, both of which belong to phylum *Firmicutes*, are reduced in individuals with bipolar disorder (29). *Faecalibacterium* is a Gram-positive butyrate-producing gut bacterium. Interestingly, both *Faecalibacterium* and *Ruminococcaceae* are relatively decreased in patients with major depressive disorder, and the reduced level of *Faecalibacterium* is correlated to the severity of depressive symptoms as measured by Hamilton's Depression Scale (56). In addition, one recent randomized controlled trial reported that adjunctive treatment with probiotics for 24 weeks was associated with a lower rate of rehospitalization in individuals with mania (57).

Major depressive disorder

One recent large cohort study shows that butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria are consistently associated with a higher quality of life indicators. While *Dialister* and *Coprococcus* bacteria were depleted in depression (58), further analysis indicated that microbial potentials were positively correlated with mental quality of life. Altered hypothalamic-pituitary-adrenal (HPA) axis (59) and elevated levels inflammation (60) may be related to the mechanism of major depressive disorder. However, microbiota could have a significant influence on both HPA axis and inflammation. In 2004, Sudo, N. et al. indicated a direct link between HPA axis and microbiota by showing that an exaggerated corticosterone and adrenocorticotropic response to stress in germ-free mice (61).

Meanwhile, increased gastrointestinal inflammation is associated with anxiety-like behavior (62) and germ-free or antibiotic treatment reduced anxiety-like behaviors in animal models (63). Several studies have indicated that the alterations in microbiota are related to anxiety and depressive-like behaviors (64). When transplanting human fecal samples from people with major depressive disorder to GF mice, the recipients exhibit depressive-like behaviors compared to controls (65). One study demonstrated that feeding healthy mice with *L. rhamnosus* bacteria could decrease anxiety-like and depressive-like behaviors (40), while in a similar study, the treatment with *B. infantis* bacteria showed reduction in depressive-like symptoms in rats (66). However, the clinical studies of the impact of probiotics on mood disorders are still in the early stages.

Autism spectrum disorder

Li et al. have reviewed recent evidence that gut microbiome may affect the risk of ASD, and gut microbiota plays

an important role in mediating the risk of ASD (67) when individuals are exposed to various adverse environmental factors in particular during prenatal and perinatal period (68). Reports have shown that the gut bacterial communities are different between individuals with ASD and typically developing controls (69, 70). The valproic acid (VPA)-induced rat model of autism presents with gut bacterial dysbiosis similar to that in human autism (71). While studies have been inconsistent, the richness of different species and diversity between ASD and TD controls are repeatedly reported.

In a recent study, Sharon et al. transplanted gut microbiota from human donors with ASD or TD controls into germ-free mice and revealed that colonization with ASD microbiota could induce hallmark autistic behaviors in germ-free mice. Additionally, particular candidate microbial metabolites could improve abnormal behaviors in the BTBR (Black and Tan Brachyury) mice model of ASD. They proposed that gut microbiota regulated behaviors through the production of neuroactive metabolites and thus contributed to the pathophysiology of ASD (72). Given the neurodevelopmental origin of ASD, maternal environment is also of great importance (68). Buffington et al. showed that maternal high-fat-diet-induced dysbiosis negatively affected the offspring's social behavior by altering signaling in the mesolimbic reward system. Interestingly, transferring the microbiota from control mice into offspring of high fat diet-fed mothers completely corrected the impairments in sociability and social novelty (73).

Moreover, a recent meta-analysis of nine studies with 254 patients showed children with ASD tend to have a low percentage of *Akkermansia*, *Bacteroides*, *Bifidobacterium*, and *Parabacteroides*, but a higher rate of *Faecalibacterium* among the detectable bacteria in the gut microflora compared to controls (74).

ANTI-PSYCHOTICS INDUCED WEIGHT GAIN AND GUT MICROBIOTA

The second-generation antipsychotics (SGA) are the mainstream treatment for schizophrenia and bipolar disorder. However, almost all antipsychotics induce weight gain (75, 76), and the risk for type 2 diabetes is significantly elevated in individuals who used antipsychotic medications (77), in particular, olanzapine and clozapine (9). In the early stage of schizophrenia, the risk for cardiovascular disease, diabetes, and pre-diabetes is lower than that in chronic schizophrenia, which is likely due to antipsychotic-induced weight gain (78).

Human-target non-antibiotic drugs such as antipsychotics may have antibiotic-like side effects on gut microbiota. In a systematic screen on 1000-marketed drugs against 40 gut microbial strains in vitro, Maier et al. reported that 24% of non-antibiotics, including all class of human medicines, inhibited the growth of at least one strains, and the chemically diverse antipsychotics were over-represented (25). Antipsychotics may alter composition of gut microbiota and induce body weight gain and metabolic disturbance (79). The potential mechanism of antipsychotic-induced metabolic disturbance could be due to the interactions bet-

ween antipsychotics and neurotransmitter receptors, altered eating habits or appetite increase, a different expression of orexigenic and anorexigenic neuropeptides, histamine H1 receptor-mediated hypothalamic AMPK activation, increased blood leptin, ghrelin and pro-inflammatory cytokines (80).

Olanzapine is one of the widely used antipsychotics that may induce the most metabolic disturbance in patients with schizophrenia. Davey et al. reported an increase in *Firmicutes* and a decrease in *Bacteroidetes*, reduced microbiota diversity, and significant weight gain in female Sprague Dawley rats after administered with olanzapine (81). Interestingly, co-administration of antibiotic cocktail in olanzapine-treated rats attenuated body weight gain and metabolic dysfunction (82). However, in germ-free mice, no significant difference in body weight was observed between a high-fat diet and high fat plus olanzapine (83). Microbial colonization of the gut, the olanzapine group gained significantly more weight than did the placebo group. This demonstrates that gut microbiota were necessary and sufficient for the occurrence of olanzapine-induced weight gain.

Risperidone, also a commonly used antipsychotics, may have a significant impact on weight gain due to the suppression of energy expenditure, which correlated with an altered gut microbiome in mice (84) and children (85). Risperidone inhibited the growth of cultured fecal bacteria, particularly those are grown anaerobically rather than aerobically. Transplantation of the fecal phage fraction from risperidone treated mice to naïve recipients caused excess weight gain through reduced energy expenditure (84). A study showed that patients with drug-naïve first-episode schizophrenia treated with risperidone for 24 weeks had a significant increase in body weight and in the numbers of fecal *Bifidobacterium* and *Escherichia coli* but had decreases in the number of fecal *Clostridium coccooides* and *Lactobacillus*, of which only increase in fecal *Bifidobacterium* are associated with the weight gain (86). However, previous study investigating the effect of risperidone on microbiome structure in males indicated a decreased ratio of bacteroidetes to Firmicutes in those chronic treated psychiatric children compared with those antipsychotic-naïve controls (85).

One study suggested that people with bipolar disorder who were treated with SGAs had decreased Simpson diversity and change in specific gut microbiota with significant weight gain compared to those who did not receive a treatment with SGAs (87). So far, most of the studies have focused on olanzapine and risperidone, the two commonly used SGAs with higher efficacy (88) but more likelihood of induced metabolic disturbance. These studies may provide evidence for a clinical translational research in human patients.

PROBIOTIC AND PREBIOTIC AS INTERVENTION

Probiotics

In 1907, Élie Metchnikoff from the Pasteur Institute proposed lactic acid bacteria being beneficial to human health (90). The term "probiotics" which derived from the Greek

word meaning "for life" first appeared in 1974. Its definition evolved over the time, and the latest consensus definition was termed by the Food and Agriculture Organization of the United Nations (FAO) and WHO as "Live microorganisms which when administered in adequate amounts confer a health benefit to the host" (89). In humans, lactic acid bacteria are the most widely used probiotics, and they mainly include *Lactobacillus*, *Enterococcus*, *Pediococcus*, *Streptococcus*, *Lactococcus*, *Leuconostoc*, and *Oenococcus*. Microorganisms claimed with probiotic properties include specific probiotic strains of the following genera of *Lactobacillus*, *Bifidobacterium* (also known as *Lactobacillus bifidus* before 1960), *Saccharomyces*, *Enterococcus*, *Streptococcus*, *Pediococcus*, *Leuconostoc*, *Bacillus*, *Escherichia coli* (91-93), in which *Lactobacillus* and *Bifidobacterium* are the most common in the gut microbiota (94) (Table 1).

Table 1. The most frequently used microorganisms as probiotics.

<i>Lactobacillus</i>	<i>Bifidobacterium</i>	Other lactic acid or other bacteria*
<i>L. acidophilus</i>	<i>B. animalis</i>	<i>Enterococcus faecalis</i>
<i>L. casei</i>	<i>B. bifidum</i>	<i>Enterococcus faecium</i>
<i>L. crispatus</i>	<i>B. infantis</i>	<i>Escherichia coli</i> Nissle
<i>L. gasseri</i>	<i>B. lactis</i>	<i>Lactococcus lactis</i>
<i>L. reuteri</i>	<i>B. adolescentis</i>	<i>Pediococcus acidilactici</i>
<i>L. rhamnosus</i>	<i>B. breve</i>	<i>Streptococcus thermophilus</i>
<i>L. paracasei</i>	<i>B. longum</i>	<i>Saccharomyces boulardii</i>
<i>L. bulgaricus</i>		<i>Saccharomyces cerevisiae</i>
<i>L. fermentum</i>		<i>Bacillus cereus</i>
<i>L. johnsonii</i>		<i>Bacillus subtilis</i>
<i>L. lactis</i>		
<i>L. plantarum</i>		
<i>L. prausnitzii</i>		

Probiotic supplements have been used in clinical practice for the prevention and treatment of several medical conditions, particularly for gastrointestinal diseases and benefits for general health (95). Different *Lactobacillus* strains can help treat diarrhea and have benefits for people who cannot digest lactose or sugar in milk. *Bifidobacterium* can be found in some dairy products and help ease the symptoms of irritable bowel syndrome (IBS) and some other conditions.

Probiotic supplements can attenuate obesity through members of the genus *Lactobacillus* (96, 97) and *Bifidobacterium* (98, 99). In animal models of obesity, certain distinctive strains of *Lactobacillus* and *Bifidobacterium* species help reducing obesity. One recent review suggests that supplementation of the probiotics mentioned above in mice and rats lead to less weight gain, fat accumulation, and adipose tissue compared to the placebo group (100). Clinically, several strains of *Lactobacillus* showed beneficial effect against metabolic dysfunction. For example, compared with those who received placebo, pregnant women who received *L. rhamnosus* supplements from four weeks before the date of expected delivery to six months of postnatally had a significant modulation of the weight gain in their children during the first few years, based on a follow-up study of the cohort from birth to 10 years (101). *L. gasseri* SBT2055, when administered to obese individuals, can significantly lower abdominal adiposity and body weight in 12 weeks (102). In addition, *B. lactis* HN019 showed a beneficial effect on reducing obesity, blood lipids, and specific inflammatory markers when administered to people with metabolic dysfunction (103). When combined, both species of *Lactobacillus* and *Bifidobacterium* as probiotic yogurt significantly reduced body weight and body mass index (BMI) in individuals with metabolic syndromes (104). Furthermore, *Bacteroides uniformis* (105) and *Akkermansia muciniphila* (106) have been identified as benefi-

cial probiotics for metabolic dysfunction, adipose tissue inflammation, and insulin resistance.

Some studies have shown that *L. plantarum* DSM15313 (107), *B. animalis subsp lactis* BB-12 (108), and *B. M13-4*(109) have excellent properties as probiotics and improves digestion, immunity and gastrointestinal health. *L. plantarum* is a helpful probiotic that can attack pathogenic and harmful bacteria and survives stomach acid with ease; while *B. animalis subsp lactis* BB-12 may have pathogen inhibition, barrier function enhancement, and immune interaction properties, and clinically has demonstrated benefits for gastrointestinal health and immune function.

Probiotics may attenuate symptoms of anxiety and depression, and be beneficial for antipsychotics-induced weight gain. Ryo Okubo et al. reported that the addition of the treatment of *B. breve* A-1 in individuals with schizophrenia could improve anxiety and depressive symptoms, but did not mention the measure of weight (110). Probiotic supplements may help attenuate the gut discomfort in male individuals with schizophrenia (111, 112). One study of mice showed that administering of probiotic mixture VSL#3 could confer a benefit for olanzapine-induced weight gain (113); a randomized clinical trial (RCT) also showed the beneficial effects of probiotics and vitamin D supplements on metabolic profiles and psychopathological symptoms in individuals with chronic schizophrenia (114). More studies are expected to determine the potential effect of probiotics as an add-on treatment for schizophrenia on metabolic profiles and clinical psycho-pathological symptoms.

Prebiotics

The concept of prebiotics was evolving as it was elaborated in the 1990s, and the current definition typically refers to nutrient-rich and nondigestible fibers found in plants and vegetables. They can pass through intestines unchanged,

end up in the deep colon, maintain for a certain period, and can stimulate the growth and activity of health-promoting bacteria that colonize the large bowel (115). Prebiotics found in supplements are usually fibers or starches; common prebiotics include fructo-oligosaccharides (FOS), inulin, galactooligo-saccharides (GOS), and 4G-β-D-galactosylsucrose (also known as Lacto sucrose).

Prebiotics has been known to contribute to weight loss and improved metabolic parameters in overweight or obese individuals(116). One recent randomized-controlled trial with 105 overweight and obese adults, divided into rice bran, rice husk powder or placebo groups, indicated that prebiotics could lead to a decrease in weight, BMI, waist circumference and pro-inflammatory markers (117). Cani et al. reported that 2-weeks intervention of prebiotics-supplemented diet in adults could increase the levels of GLP-1 and PYY, and decrease the ratings of the hunger assessed with visual analogue scales (VAS) (41); A randomized placebo-controlled study showed that intake of inulin for 8 weeks seemed to modulate inflammation and metabolic endotoxemia in women with type 2 diabetes (118). In a one-month randomized placebo-controlled trial, de Luis et al showed that prebiotics (Inulin and FOS) together with alpha linolenic acid (ALA), the metabolic precursor of the long chain n-3 fatty acid eicosapentaenoic acid (20: 5n-3) that has anti-inflammatory properties, could improve total cholesterol, LDL cholesterol and C reactive protein levels in obese men(119). However, inconsistent effects of prebiotics were also observed (120).

The beneficial effects of prebiotics against obesity and metabolic dysfunction may be through different mechanisms. One popular hypothesis is that prebiotic supplements increase the growth of specific gut microbiota, for example, *Lactobacillus* and *Bifidobacterium*, but not pathogenic microorganisms (121). These changes might be related to better enteroendocrine cell activity, glucose homeostasis, and leptin sensitivity in obese and diabetic mice treated with prebiotics (122). Supplementation with α-cyclo-dextrins also increases lactic acid and SCFAs levels in obese mice, which is likely associated with lipid metabolism and appetite (123). Besides, the increased intestinal permeability and microbial dysbiosis in the high fat diet in mice could be prevented with an addition of prebiotics, which may be related to a beneficial effect on weight gain (124).

Only recently, a few studies have focused on the effectiveness and safety of prebiotic modulation on anti-psychotic-induced weight gain and metabolic dysfunction. Kao et al. (125) conducted a study in which adult female Sprague-Dawley rats were administered a Bimuno™ galacto-oligosaccharide (B-GOS, 0.5 g/kg/day) or water for 21 days while receiving an intraperitoneal injection of olanzapine daily on day 8 through 21. The use of B-GOS significantly attenuated olanzapine-induced weight gain, followed by a decrease in the plasma acetate concentrations, and elevation of fecal *Bifidobacterium* but reduction in bacteria in phylum *Firmicutes*. Kao et al (126) further found that the prebiotic reduction of brain histone deacetylase (HDAC) activity and OIWG in rats was independent of acetate major short-chain fatty acid (SCFA) that is produced by G-BOS

fermentation. Later, Kao et al. published a letter based on a double-blind placebo-controlled crossover study of thirty-nine non-hospitalized participants randomized to B-GOS or placebo group, in which after 24 weeks trial, the treatment group showed a significant increase in the cognitive composite T-score, which was driven by subtests of executive function. However, supplementation of B-GOS did not affect weight, BMI, central adiposity, circulating candidate metabolic or immune markers (127).

In addition, a clinical study of 16 Japanese in-patients with chronic schizophrenia suggested that Lactosucrose as a prebiotic could improve underweight accompanied by increased *Bifidobacterium* in fecal microbiota (128). However, there was a report showing no difference in body weight before and after a supplementation of resistant starch in individuals with schizophrenia (129). Further studies with adequate sample size are required to determine the potential effects of prebiotics on antipsychotic-induced weight gain and metabolic dysfunctions.

Synbiotics

Synbiotics are defined as "mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract of the host."(130) Soon after the concept of prebiotics was introduced, investigators speculated the potential benefits of combining prebiotics with probiotics. This combination was then called synbiotics (131). Although there are very few reported clinical trials of synbiotics, the limited results seem to suggest a beneficial effect on glucose and insulin metabolism (132). As far as we know, currently there is no research about the potential effect of synbiotics on anti-psychotic-induced weight gain or metabolic dysfunction.

Since recent studies have indicated that gut microbiota play an important role in an individuals' health and risk of diseases, especially metabolic dysfunction and obesity (133), it would be of interest to discover new therapeutics to treat or prevent obesity and related metabolic disorders by a modulation of the gut microbiota to mimic that found in healthy non-obese individuals. So far there have been a few published animal models (Table 2) and clinical trials (Table 3) on prebiotic and probiotic supplements in individuals with schizophrenia.

CONCLUSION AND FUTURE DIRECTIONS

In this paper, we provide a summary of the recent studies of the gut microbiota in psychiatric disorders and anti-psychotic-induced metabolic dysfunction. Bidirectional communication between the brain and the gut has recently been recognized. Patients with neuropsychiatric disorders such as schizophrenia, bipolar disorder, ASD, and major depressive disorder have different patterns of altered gut microbiota composition compared with healthy controls. It is critical to determine the role and elucidate possible mechanism by which microbiota influences the development of neuropsychiatric disorders, with more advanced study designs and adequate power. The development in sequencing technology and bioinformatics could allow us to conduct an in-depth investigation of brain and the gut inter-

relationship.

While the mechanism has yet to be elucidated, interventional study would help assess the potential benefit and safety of prebiotics and probiotics and provide causal evidence if efficacy is observed. Studies have shown effects of prebiotics or probiotics on obesity or metabolic disturbance, but few have examined the impact of probiotics in antipsychotic-induced weight gain and metabolic dysfunction. In addition, understanding the mechanism of any effective responses could help discover novel therapeutics.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this paper.

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Table 2. Animal studies of prebiotic or probiotic supplements and antipsychotics

Author	Species	N	Intervention	Result	Conclusion
Dhaliwal N,(113), 2019	Female Swiss albino LACA mice	20	Randomized into four groups: -Control -Olanzapine+VSL#3 -Olanzapine -VSL#3 Olanzapine (3 mg/kg, p.o) once daily for 28 days. Probiotic mixture VSL#3 (20*10 ⁹ CFU/day, p.o) once daily for 28 days.	VSL#3 administration attenuate OLZ-induced body weight gain, uterine fat deposition, impaired glucose tolerance, and insulin resistance. Olanzapine treatment decreased inflammatory markers, abolished oxidative stress in vWAT, and prevented shifts in gut microbiota abundance levels	VSL#3 via its ability to manipulate gut microbiome confers beneficial metabolic effects and represent a novel therapeutics for reversing antipsychotic-induced metabolic dysfunction
Kao A.C 2018	Female adult Sprague-Dawley rats	24	Randomized into four groups: -saline/water, -B-GOS®/saline, -water/ olanzapine, -B-GOS®/olanzapine. rats were given water or water plus B-GOS® (0.5 g/kg/day) for 1 week, followed by a 2-week, daily intraperitoneal injection of olanzapine (10 mg/kg) or saline, during which water or B-GOS® administration continued.	B-GOS® feeding attenuated olanzapine-induced weight gain without influencing the reduction of central 5-HT2AR levels. Olanzapine increased levels of GluN1 in the frontal cortex and GluN1 mRNA expression in CA3 with the presence of B-GOS®, Olanzapine alone or with B-GOS® did not affect the abundance of some specific genera of enteric bacteria, while B-GOS® alone had some notable effects.	B-GOS® reduced weight gain when adjunctively with second-generation antipsychotic drugs, without affecting their central molecular actions.
Kao A.C (126), 2019	Female adult Sprague-Dawley rats, 220-250g (6-8weeks),	48	Randomized to four groups: -saline/water (n=6), -acetate/saline (n= 6), -water/olanzapine (n = 6), -acetate/olanzapine (n = 6) Sodium acetate was administered to rats via their drinking water at a dose of 500mg/kg/day; Olanzapine (10 mg/kg) was intraperitoneal injected daily.	Ingestion of sodium acetate inhibited HAT activity in brain, and increased hippocampal levels of HDAC-3 and HDAC-4 mRNAs. Acetate administration did not affect olanzapine-mediated weight gain, alter the expression of NMDAR subunits, or influence abundance of fecal microbial genera.	B-GOS®-mediated benefits on central and peripheral physiology are not entirely, if at all, mediated by acetate produced from fermentation of B-GOS.

Table 3. Clinical trials of probiotic or prebiotic supplements in patients with Schizophrenia

Author, Year	Design	Subjects	Intervention	Control	Results	Conclusions
Okubo R (110), 2018	Open-label single-arm study	N=30, outpatient with schizophrenia, BPRS anxiety and depressive symptoms \geq 10 points, aged >20 years	Probiotics: 2 sachets of <i>B. breve</i> A-1 at 5.0×10^{10} colony-forming units each per day for first 4 and evaluated 4 weeks after.	No control	HADS was improved at 4 weeks but not at 8 weeks, PANSS anxiety/depression score was improved at both 4 and 8 weeks.	<i>B. breve</i> A-1 improves anxiety and depressive symptoms in patients with schizophrenia, which is related to TRANCE and IL-22.
Nagamine T (128), 2018	Open-label single-arm study	N=16, underweight Japanese schizophrenia inpatients	Prebiotics: 3.0 g/day 4G- β -D-galactosylsucrose as a food supplement for 6 months.	No control	Bodyweight and BMI Blood glucose or triglyceride level	4G- β -Dgalactosylsucrose had a weight gain effect in underweight schizophrenia inpatients accompanied by a bifidobacteria-enhancing result.
Kao KC (127), 2019	Randomized double-blind placebo-controlled crossover trial	N=39, outpatient with psychosis on stable antipsychotic medication, global cognitive score was 0.5 standard deviations below healthy average	Prebiotics: One sachet (3.5g) of galactooligosaccharides (B-GOS®) daily during breakfast for 12 weeks	Maltodextrin (3.5g) daily during breakfast for 12 weeks	Composite T-score (Cohen's $d=0.443$), Subtests of executive function, mood, anthropometric indices or serum levels of acetate, CRP and IL6	Consumption of the prebiotic B-GOS® confers significant cognitive benefits but did not affect weight, BMI, central adiposity or circulating candidate metabolic/immune markers
Dickerson FB (52), 2014	Randomized double-blind placebo-controlled trial	N=65, outpatients with schizophrenia with at least moderately severe psychotic symptoms	Probiotics: 2-week placebo run-in period, 14 weeks adjunctive probiotic tablet supplement once per day	Control tablets identical in appearance for once per day	No significant difference in PANSS total symptom score	Probiotic supplementation may help prevent a common somatic symptom associated with schizophrenia
Severance EG (111), 2017	Randomized, placebo-controlled pilot study	N=56, outpatients with schizophrenia with at least moderately severe psychotic symptoms	Probiotics: 2 weeks placebo run-in period, and 14 weeks adjunctive probiotic tablet supplement once per day	Control tablets identical in appearance for once per day	<i>C. albicans</i> IgG levels reduced in male schizophrenia with probiotics, improved bowel function	Administration of probiotics may help normalize <i>C. albicans</i> antibody levels and associated gut discomfort in male individuals
Ghaderi A (48), 2019	Randomized, double-blind, placebo-controlled trial	N=60, schizophrenia PANSS score 55 or higher, treated with chlorpromazine and anticholinergic	Probiotics: 50,000 IU of vitamin D3 every 2 weeks plus 8×10^9 CFU/day of probiotics for 12 weeks	Capsules in a similar shape and packaging as vitamin D and probiotics for 12 weeks	25-OH-vitamin D levels, PANSS scores; Plasma TAC and decreased MDA; FPG, serum insulin concentrations, HOMA-IR, triglycerides, cholesterol, HDL	Probiotic and vitamin D for 12 weeks had impacts effects on the general and total PANSS scores, as well as other metabolic profiles.
Tomasik J (112), 2015	Randomized double-blind placebo-controlled trial	N=65, outpatients with schizophrenia at least moderately severe psychotic symptoms	Probiotics: 2 weeks placebo run-in period, and 14 weeks adjunctive probiotic supplement daily	Control tablets identical in appearance for once per day	levels of MCP-1, BDNF, T-cell-specific protein RANTES	Probiotics have immunomodulatory effects in schizophrenia patients and improve bowel functioning through IL-17-related immune responses.
Flowers SA (129), 2019	Cross-sectional cohort study	N=37, adults with a diagnosis of bipolar disorder or schizophrenia who were treated with an AAP or lithium and/or lamotrigine	Prebiotics: raw, unmodified potato starch (resistant starch) daily (48 g/day)	No control	Actinobacteria phylum increased with resistant starch administration. Increase in the OTU corresponding to resistant starch degrading. Inverse Simpson Diversity Index.	Resistant starch supplements increased organisms associated with starch degradation and SCFA.

HADS, Hospital Anxiety and Depression Scale.

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