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REVIEW ARTICLE

Potential relationship between Tourette syndrome and gut microbiome

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Abstract

Objective: In this article, the author aims to discuss and review the relationship between gut microbiota and Tourette syndrome, and whether the change in gut microbiota can affect the severity of Tourette syndrome.

Sources: Literature from PubMed, Google Scholar, and China National Knowledge Infrastructure was mainly reviewed. Both original studies and review articles were discussed. The articles were required to be published as of May 2022.

Summary of the findings: Current studies on the gut microbiome have found that the gut microbiome and brain seem to interact. It is named the brain-gut-axis. The relationship between the brain-gut axis and neurological and psychiatric disorders has been a topic of intense interest. Tourette syndrome is a chronic neurological disease that seriously affects the quality of life of children, and there appears to be an increase in *Ruminococcaceae* and *Bacteroides* in the gut of patients with Tourette syndrome. After clinical observation and animal experiments, there appear to be particular gut microbiota changes in Tourette syndrome. It provides a new possible idea for the treatment of Tourette syndrome. Probiotics and fecal microbial transplantation have been tried to treat Tourette syndrome, especially Tourette syndrome which is not sensitive to drugs, and some results have been achieved.

Conclusions: The relationship between gut microbiota and Tourette syndrome and how to alleviate Tourette syndrome by improving gut microbiota are new topics, more in-depth and larger sample size research is still needed.

Introduction

Tourette syndrome (TS) is a chronic neurological disease, which is common in children. As one of the most serious subtypes of tic disorder (TD), the symptoms of TS include

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uncontrolled stereotyped movements and special sounds (which can occur alternately), and the total duration of the disease is more than 1 year.[1] Epidemiology shows that the incidence rate of TS in children is about 0.5%-0.8%.[2,3] Although it is generally believed that most patients can recover by themselves before the age of 18, in fact, about 1/3 of patients will continue their symptoms to adulthood. At present, it is considered that the overall prevalence rate of adults is about 0.01% - 0.09%.[3] TS with severe symptoms may have uncontrollable obscene behavior and obscene speech (coprolalia), which will seriously affect the patient's quality of life and normal social activities.[1,4] More effective treatments are needed now.

The existing treatment methods mainly include non-drug treatment and drug treatment Non-drug treatment mainly includes comprehensive behavioral intervention for tics (CBIT), psychoeducation and supportive therapy (PST),[5] acupuncture, etc.[6] However, because the above treatment methods need the guidance of professionally trained doctors and the active cooperation of patients (more suitable for patients over 9 years old), the beneficiary population is relatively small. At present, the drugs widely used in the treatment of TS mainly include dopamine modulating agents, alpha-2-adrenergic agonists, GABAergic medicines, and other atypical neuroleptics; the development of the above drugs is mainly based on the main etiology of TS, neurotransmitter disorder, especially the disinhibition of the Cortical-Striatum-Thalamus-Cortical Circuits. These drugs can alleviate tic symptoms by adjusting neurotransmitter levels and changing receptor sensitivity. Since most patients are children, their nervous system is not fully developed, and nervous system drugs are easy to affect their normal development. Only a few drugs are recommended by national guidelines, such as haloperidol, pimozide, aripiprazole, and tiapride.[7,8] Even so, a large number of adverse events have been reported, including sedation, dizziness, drowsiness, muscle tremor, dyskinesia, other extrapyramidal symptoms, and metabolic syndrome.[9] At the same time, because the total course of treatment may be more than one year (sudden or rapid withdrawal may lead to the aggravation of tic symptoms), this poses a great challenge to the mental pressure and economic burden of patients. Now more effective and safer methods are needed, especially for TS with severe symptoms and poor response to drugs.

In recent years, the relationship between intestinal microorganisms and nervous system diseases has gradually attracted the attention of scholars all over the world.[10,11] Intestinal microorganisms in the human body include bacteria, archaea, microbial, eukaryotes, fungi, and viruses, with a total number of 10^{13} to 10^{14}, of which the total weight of bacteria in the adult intestine can reach 1kg. These microorganisms contain 100 times or more genes than human cells do.[12] The abundance, quantity and ratio of gut microbes are dynamic and influenced by many factors. The human body can limit oxygen access to the intestinal lumen in a number of ways to maintain a physiologic hypoxic state in the intestinal lumen.[13] Intestinal microorganisms can affect the activity of enzymes and thus the synthesis of neurotransmitters. Some of their metabolites can repair the nervous system and protect the blood-brain barrier. They can also reduce or increase the secretion of inflammatory factors by affecting the increment and recruitment of immune cells, so as to change the inflammatory state of the intestinal and nervous systems. Alterations in the gut microbiota appear to correlate somewhat with the severity of many neurological diseases, such as autism spectrum disorder (ASD), Parkinson's disease (PD), depression, and epilepsy.[14–17] At the same time, fecal microbiota transplantation (FMT) seems to improve the symptoms of these neurological diseases. It provides a new idea for the treatment of TS.

The aims of this review were as follows: (1) to explore whether there are gut microbiota changes in patients with TS; (2) whether such changes are characteristic; (3) brief discussion of antipsychotic medications on gut microbiota; (4) to discuss the current state of research on oral probiotics and FMT for the treatment of TS.

Retrieval strategy and method

Literature from PubMed, Google Scholar, and China National Knowledge Infrastructure was mainly reviewed. Keywords include but are not limited to tic disorder, Tourette syndrome, gut microbiota, intestinal flora, brain-gut axis, fecal microbial transplantation, and probiotics. The articles were required to be published as of May 2022. Two researchers (Junze Geng, Can Liu) screened the retrieved literature. If there were differences, the third researcher (Xinmin Li) would decide whether to include the literature in the discussion. Finally, 8 articles met the requirements, including 3 animal experiments with 5 clinical types of research.

Brain-gut axis

Existing studies show that not only the brain can regulate gastrointestinal function and homeostasis, but also the intestine can affect people's mood, sleep, and even the development and repair of the nervous system in a variety of ways. This two-way communication between the brain and intestine is called BGA.[16,18] The realization of this two-way communication is mainly through the regulation of the neuroimmune endocrine system, in which the central nervous system (CNS), autonomic nervous system, enteral nervous system (ENS), and hypothalamic-pituitary-adrenal (HPA) axis are all involved. A variety of neurotransmitters are synthesized in the gastrointestinal tract, including serotonin (5-HT), dopamine, epinephrine, norepinephrine, and γ-aminobutyric acid (GABA). They are introduced into CNS through ENS to affect the physiological function of the brain. Gut microbiota can affect the production of neurotransmitters by changing the activity of enzymes in the neurotransmitter synthesis pathway or competitive consumption of neurotransmitter precursors, such as tryptophan.[19] Existing studies have found that *Lactobacillus* and *Bifidobacterium* affect the synthesis of acetylcholine and GABA, and the synthesis of serotonin, dopamine, and norepinephrine is affected by *Streptococcus*, *Enterococcus*, and *Escherichia*.[14,20,21] At the same time, products produced by microbial metabolisms, such as short-chain fatty acid (SCFA), can affect the development of a nervous system and immune signal transmission. Through the comparison of germ-free mice, mice treated with antibiotics, and normal mice, it is found that the damage of gut microbiota will

reduce the maturity and number of microglia and astrocytes, thus affecting the immune function and signal transmission of the central nervous system.[22,23]

The gastrointestinal tract is considered as the interface where the human body has the greatest contact with the external environment. And the intestinal mucosa is the first barrier between the human body and the intestinal lumen before, and its proper function or not affects the body to the intestinal lumen for material exchange and the invasion of pathogens.[24] Bacteria living in the intestine can change the barrier effect of intestinal mucosa by promoting inflammatory response and degrading biofilm on the mucosal surface.[25] At the same time, many drugs, such as aripiprazole, have also been reported to change the mucosal barrier of the intestine,[26] which may lead to changes in signal transmission between brain and intestine.

Characteristics of gut microbiota in patients with TS

Wang detected the gut microbiota of 40 children with TS and compared them with healthy children at the phylum level. The results showed that the relative abundance of *Firmicutes* in the feces of patients with TS was less than that of healthy children; on the contrary, the relative abundance of *Proteobacteria* increased. After one month of acupuncture and massage treatment (87.5% of TS patients' symptoms were significantly improved), the fecal microbial characteristics of the two groups were compared again. The results showed that the fecal microbial characteristics of the two groups were similar. Wang's study illustrated a possible disturbance of gut microbiota in patients with TS and that improvement of gut microbiota may have a correlation with an improvement of tic symptoms.[27]

Xi conducted a more in-depth study. He compared the fecal microorganisms of 35 TD children who had not received drug treatment with those of healthy children. The results showed that compared to healthy children, treatment-naive TD children had significantly higher abundances of *Bacteroides plebeius* and *Ruminococcus lactaris* and lower abundances of *Prevotella stercorea* and *Streptococcus lutetiensis*; among them, children with TS have a significant increase in *Ruminococcus lactaris*, which is different from children with a chronic tic disorder. They show a higher level of *Bacteroides plebeius*.[28] Xi also analyzed the composition of fecal microorganisms in 12 TD children treated with dopamine receptor antagonist (DRA). The results showed that there was no significant difference in fecal microorganisms between these children and TD children and healthy children, which may indicate that the fecal microorganisms of TD children are approaching healthy children after drug use. The three groups of children were compared at the same time. It was found that there were significantly more *Bacteroides plebeius* and *Ruminococcus lactaris* in treatment-naive children, which were considered to be related to a variety of autoimmune diseases.[29−31] This suggests that *Ruminococcus lactaris* and its metabolites may be involved in oxidative stress and promote the production and aggregation of inflammatory factors.[31] In addition to this, Xi found that the level of GABA degradation was significantly increased in TD children with or without previous medication, and the gut microbiota was changed correspondingly. *Klebsiella pneumoniae*, a GABA-degrading bacteria,[32] showed a positive correlation with the deterioration of TD symptoms, and the *Eubacterium spp.*, *Bifidobacterium spp.*, and *Akkermansia muciniphila*, which were considered to be related to GABA production,[33,34] were more significantly negatively correlated with YGTSS score. But there are exceptions. Several bacteria of the *Bacteroides* genus, such as *B. thetaiotaomicron* and *B. eggerthii* were positively correlated with the increase of YGTSS score, even if they were recognized as GABA producers.[28]

In order to verify the association between gut microbiota and TS, Li conducted an animal experiment.[35] He used 3,3'-iminodipropiononitrile (IDPN) to establish TS mouse models and analyzed the fecal microorganisms of TS mice and healthy mice, which underwent fecal microbiota transplantation (FMT) with feces from TS mice (HTSM). The results showed that the relative impairment of *Turicibacteraceae* and *Ruminococcaceae* in TS mice was significantly increased compared with healthy mice. In HSTM, the levels of *Firmicutes* and *Actinobacteria* decreased, and *Bacteroidetes* and *Proteobacteria* increased. Li's experimental results are similar to Wang's clinical trial results. But unfortunately, Li didn't report whether there was twitch behavior in HTSM, which only shows that there are changes in gut microbiota in TS mice, and this change can be infectious. Because the impact of ipdn on gut microbiota can not be ignored, the authors can not accurately judge the relationship between twitch behavior and gut microbiota changes. Based on the above, whether the abnormal change of gut microbiota is the key factor of TS remains to be further studied.

Effect of antipsychotic medications on gut microbiota

The effect of antipsychotic medications is not only on the nervous system. Because they are mostly taken orally, their effect on gut microbiota may be earlier than that on the nervous system. In fact, there have been some reports on the antibacterial ability of antipsychotic medications. For example, in vitro experiments have proved that sertraline has an antibacterial effect on *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.[36,37] The effect of psychotic drugs on gut microbiota may lead to the change of disease and the occurrence of gastrointestinal adverse events. The drugs commonly used in the treatment of TS mainly include aripiprazole, risperidone, and a variety of DRA drugs.[26,38] Most of them have a certain impact on gut microbiota.[39,40]

Studies have shown that aripiprazole can induce an increase in *Firmicutes*, particularly *Ruminococcus*. At the same time, it enhances the permeability of the ileum,[41] which may affect the barrier function of the intestinal mucosa. Long-term use of risperidone will reduce the *Bacteroidetes: Firmicutes* ratio and affect the metabolism of butyrate and propionate, which may lead to higher levels of SCFA production, leading to weight gain.[42] The effect of DRA drugs on the gut microbiota of TS children is not limited to bringing them closer to healthy children. At the same time,

DRA drugs improve the levels of several potential pathogenic bacteria, such as *Bacteroides dorei*, E*scherichia coli*, *Bacteroides caccae*, and *Ruminococcus gnavus*. It affects the metabolic function of the gut microbe and then affects the nervous system. Specifically, it includes the significant reduction of L-tryptophan biosynthesis, mannan degradation and pyruvate fermentation, the significant increase of 3-phenylpropionate, and 3-(3-hydroxyphenyl) propionate degradation, enterobactin biosynthesis, and fatty acid beta-oxidation.[28]

The discussion of the effects of antipsychotic medications on gut microbiota is mostly based on studies of other neurological and psychiatric disorders, and whether their distinct effects on gut microbiota in children with TS still warrant further investigation.

Treatment of TS acting on gut microbiota

Oral probiotics

Based on the existence of abnormal intestinal microorganisms in TS children, scholars have begun to explore whether oral probiotics can relieve tics symptoms in animal experiments and clinical trials. Liu used *Lactobacillus plantarum* PS128 (PS128), a probiotic that has been shown to ameliorate anxiety-like behaviors in naive mice and germ-free mice,[43,44] for the treatment of TS rats, a 2,5-Dimethoxy-4-iodoamphetamine (DOI)-induction model. The results showed that PS128 could significantly improve the twitch behavior of rats, compared with the blank control group, PS128 increased *Bacteroidaceae* in rats, especially *Prevotellaceae*, and decreased the level of *Lachnospiraceae* in *Firmicutes*.[45] The experimental results also showed that PS128-fed rats not only presented with elevated dopamine (DA) metabolites but were resistant to DOI-induced DA changes, which illustrated that PS128 might enhance the stability of the dopamine system in rats. The flora changes found in this experiment are slightly different from others, which may be because the TS-inducing drug used in this experiment is DOI, not IPDN. This also suggests that different TD types may have different characteristics of gut microbiota, which may need to be further studied in the future. It is important to note that findings from animal experiments can only be investigated as possible mechanisms and cannot account for the mechanism of action of probiotics in humans. At present, much remains to be learned about the mechanisms of action and therapeutic effects of probiotics in humans.

Wang conducted a 12-week randomized controlled trial involving 130 TS children.[46] All participants were divided into three groups and treated with tiapride (tiapride group), Live Combined Bifidobacterium, Lactobacillus and Enterococcus Capsules, Oral (probiotics group), and tiapride + probiotics (combined treatment group). The results showed that compared with the other two groups, the combined treatment group improved the Yale Global Tic Severity Scale (YGTSS) score of TS children most significantly (12.60 ± 4.51 vs 14.92 ± 5.98 vs 21.12 ± 6.88). The improvement of the probiotics group is the least. The results showed that oral probiotics could be considered as an adjunctive treatment for the treatment of TS, and the effect of probiotics taken alone was not significant.

FMT

Although oral probiotics can affect the gut microbiota, the effect is not obvious because they need to be taken for a long time and are affected by diet, probiotic types, and other factors. FMT, as a treatment still under exploration, has been tried to be applied to a variety of refractory nervous system diseases with intestinal microbiological abnormalities, such as ASD,[47] PD,[48] epilepsy.[49] In recent years, Zhao's team tried to use FMT for TS. The first case of TS treated with FMT was reported in 2017.[50] A 9-year-old male patient with a total course of 2.5 years still had convulsive symptoms after treatment with herbal medicine and tiapride. After taking probiotics and tiapride, he was relieved for about 6 months, although the tic symptoms became serious later, suggesting that the child may have gut microbiota disorder, which made Zhao consider the feasibility of FMT. The feces for treatment came from a 14-year-old healthy boy after screening. The prepared fecal microbial suspension was applied to the patient's small intestine and colon through gastroscopy and enteroscopy. After FMT, patients were still required to take 100mg of tiopride orally every day. Before treatment, the patient's YGTSS score was 31, and in the 8th week after treatment, the YGTSS score decreased to 5 The parents of the child said that tic behavior was hardly observed, and the child's attention was more focused than before. This shows that FMT has a certain therapeutic effect on TS. Subsequently, Zhao treated 5 male children diagnosed with TS with FMT,[51] and the specific treatment method was the same as before.[50] The results showed that the YGTSS score of 4 children decreased by more than 25%, ranging from 7 to 35, and 2 patients said that the symptoms disappeared completely. However, one participant's YGTSS score increased by 4. This may indicate that FMT is not applicable to all children with TS, or the changes in gut microbiota are complex, and its effect on TS needs to be further studied. Although only 6 cases of TS treated with FMT have been reported, it still provides a new idea for the treatment of TS in the future.

Li conducted an animal experiment to verify the effect of FMT on the gut microbiota of TS mice.[38] He transplanted the feces of healthy mice into TS mice to alleviate the symptoms of TS mice. At the same time, after completing FMT, the serum 5-HT level of TS mice increased, which indicates that FMT can regulate the production of neurotransmitters by improving gut microbiota, so as to treat TS.

Deficiency and outlook

The relationship between gut microbiota and TS began to be deeply studied in recent 5 years. This may be related to fewer reports of gastrointestinal symptoms such as abdominal pain, abdominal distension, and constipation in TS children. The reason may be that children's perception and expression of the above sensory symptoms are not significant or easy to be ignored. At the same time, the change in gut microbiota may be more reflected in its impact on the nervous system, emotion (such as irritability, hyperactivity, autism, etc.), and personality. Existing studies have shown that patients with TS do have gut microbiota disorders, including the increase of *Ruminococcaceae* and *Bacteroides*, especially *Ruminococcus lactaris* and *Bacteroides plebeius*.

However, whether the analysis of gut microbiota can be used as one of the specific diagnostic criteria remains to be considered and further verified. On the other hand, whether the abnormal changes in gut microbiota can cause TS remains to be verified. Although Li tried to transplant the feces of TS mice to healthy mice, there were no reports of twitching in healthy mice, which needs further animal experiments. In fact, the relationship between gut microbiota and neurological development and neurological diseases in children remains to be further explored. The diversity and richness of gut microbes are influenced by many factors, including genetic factors, drugs, dietary habits, diseases, taking probiotics, and so on. This makes the relationship between gut microbes and the nervous system quite complex and requires further study. The mechanisms of action of probiotics and FMT on disease are also obscure and require intensive study and cautious use.

There are more and more reports on the treatment of TS based on gut microbiota. FMT and probiotics are tried to be used in the treatment of TS. Interestingly, acupuncture, massage, and herbal medicine have also been proved to treat TS by affecting the gut microbiota. Wang alleviated the symptoms of 35 TS children (35/40) through acupuncture and massage. At the same time, it was found that after the treatment was effective, his gut microbiota was also close to the characteristics of gut microbiota of healthy children.[27] This is noteworthy, indicating that not only diet and drugs can affect the gut microbiota, but there may be many undiscovered mechanisms. Qinglong Zhidong Decoction, a traditional Chinese medicine prescription, has been shown to regulate the composition of the intestinal microbiota by increasing the abundance of *Lactobacillus* and *Bacteroides*, but reducing the abundance of *Alloprevotella* and *Akkermansia* to treat TS.[52] This provides a new idea, including the use of probiotics, FMT, and other ways to influence the gut microbiota to treat TS. From the existing research, it is found that these treatment methods have almost no adverse events, which has great advantages and great development potential compared with antipsychotics. This is beneficial to the treatment of TS patients who are not sensitive to drugs, especially because the change in gut microbiota is related to human drug tolerance.[53–55] Of course, because FMT and other methods are rarely reported in the treatment of TS, and most of them are small sample studies, their effectiveness and safety still need to be proved by larger clinical trials and animal experiments.

Conclusions

Existing studies suggest that changes in the gut microbiota appear to be present in children with TS, but because there are fewer studies, the outcome is subject to further consideration. Therapies targeting the gut microbiota seem to be able to effectively improve tic symptoms. But studies on the characteristics of gut microbiota in patients with TS, how the gut microbiota affects the severity of TS, and the efficacy and safety of FMT in treating TS still need to be explored in depth in more multicenter, large sample size studies.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Cohen SC, Leckman JF, Bloch MH. Clinical assessment of Tourette syndrome and tic disorders. Neurosci Biobehav Rev. 2013;37:997–1007.
2. Hartmann A, Worbe Y, Black KJ. Tourette syndrome research highlights from 2019. F1000Res. 2020;9:1314.
3. Hartmann A, Worbe Y, Black KJ. Tourette syndrome research highlights from 2017. F1000Res. 2018;7:1122.
4. Weingarden H, Scahill L, Hoeppner S, Peterson AL, Woods DW, Walkup JT, Piacentini J, Wilhelm S. Self-esteem in adults with Tourette syndrome and chronic tic disorders: The roles of tic severity, treatment, and comorbidity. Compr Psychiatry. 2018;84:95–100.
5. Jimenez-Shahed J. Medical and Surgical Treatments of Tourette Syndrome. Neurol Clin. 2020;38:349–66.
6. Geng JZ, Xu JY, Wang XG, Liu YQ, Cui YN, Li XM. Acupuncture: a new method to treat tic disorders in children. Tradit Med Res. 2022;7:16.
7. Liu ZS, Cui YH, Sun D, Lu Q, Jiang YW, Jiang L, et al. Current status, diagnosis, and treatment recommendation for tic disorders in China. Front Psychiatry. 2020;11:774.
8. Roessner V, Eichele H, Stern JS, Skov L, Rizzo R, Debes NM, et al. European clinical guidelines for Tourette syndrome and other tic disorders-version 2.0. Part III: pharmacological treatment. Eur Child Adolesc Psychiatry. 2022;31:425–41.
9. Ueda K, Black KJ. A comprehensive review of tic disorders in children. J Clin Med. 2021;10:2479.
10. Zhang Y, Zeng Y, Nie X. Research progress of the application of fecal microbiota transplantation in pediatric diseases. Chin J Appl Clin Pediatr. 2022;37:311–4.
11. Vendrik KE, Ooijevaar RE, de Jong PR, Laman JD, van Oosten BW, van Hilten JJ, et al. Fecal microbiota transplantation in neurological disorders. Front Cell Infect Microbiol. 2020;10:98.
12. Jang SH, Woo YS, Lee SY, Bahk WM. The brain-gut-microbiome axis in psychiatry. Int J Mol Sci. 2020;21:7122.
13. Tiffany CR, Bäumler AJ. Dysbiosis: from fiction to function. Am J Physiol Gastrointest Liver Physiol. 2019;317:G602–8.
14. Saurman V, Margolis KG, Luna RA. Autism spectrum disorder as a brain-gut-microbiome axis disorder. Dig Dis Sci. 2020;65:818–28.
15. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol. 2015;21:10609–20.
16. Liang S, Wu X, Hu X, Wang T, Jin F. Recognizing depression from the microbiota–gut–brain axis. Int J Mol Sci. 2018;19:1592.
17. Socała K, Doboszewska U, Szopa A, Serefko A, Włodarczyk M, Zielińska A, et al. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res. 2021;172:105840.
18. Gershon MD, Margolis KG. The gut, its microbiome, and the brain: connections and communications. J Clin Invest. 2021;131:e143768.
19. Mittal R, Debs LH, Patel AP, Nguyen D, Patel K, O'Connor G, et al. Neurotransmitters: the critical modulators regulating gut-brain axis. J Cell Physiol. 2017;232:2359–72.
20. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13:701–12.
21. Galland L. The gut microbiome and the brain. J Med Food. 2014;17:1261–72.
22. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation

and function of microglia in the CNS. Nat Neurosci. 2015;18:965–77.
23. Osadchiy V, Martin CR, Mayer EA. The gut-brain axis and the microbiome: mechanisms and clinical implications. Clin Gastroenterol Hepatol. 2019;17:322–32.
24. Takiishi T, Fenero CI, Câmara NO. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. Tissue Barriers. 2017;5:e1373208.
25. Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. Cell. 2016;167:1339–53. e21.
26. Cussotto S, Strain CR, Fouhy F, Strain RG, Peterson VL, Clarke G, et al. Differential effects of psychotropic drugs on microbiome composition and gastrointestinal function. Psychopharmacology (Berl). 2019;236:1671–85.
27. Wang Z. Effect of pediatric massage combined with acupuncture on gut microbiota structure of children with Tourette Syndrome. Inner Mongolia Medical University; 2021, MA thesis.
28. Xi W, Gao X, Zhao H, Luo X, Li J, Tan X, et al. Depicting the composition of gut microbiota in children with tic disorders: an exploratory study. J Child Psychol Psychiatry. 2021;62:1246–54.
29. Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med. 2015;21:895–905.
30. Mondot S, Lepage P, Seksik P, Allez M, Tréton X, Bouhnik Y, et al. Structural robustness of the gut mucosal microbiota is associated with Crohn's disease remission after surgery. Gut. 2016;65:954–62.
31. Hynönen U, Rasinkangas P, Satokari R, Paulin L, de Vos WM, Pietilä TE, et al. Isolation and whole genome sequencing of a Ruminococcus-like bacterium, associated with irritable bowel syndrome. Anaerobe. 2016;39:60–7.
32. Sanchez M, Fernández J, Martin M, Gibello A. Garrido-Pertierra A. Purification and properties of two succinic semialdehyde dehydrogenases from Klebsiella pneumoniae. Biochim Biophys Acta. 1989;990:225–31.
33. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, et al. GABA-modulating bacteria of the human gut microbiota. Nat Microbiol. 2019;4:396–403.
34. Yunes RA, Poluektova EU, Dyachkova MS, Klimina KM, Kovtun AS, Averina OV, et al. GABA production and structure of gadB/gadC genes in Lactobacillus and Bifidobacterium strains from human microbiota. Anaerobe. 2016;42:197–204.
35. Li H, Wang Y, Zhao C, Liu J, Zhang L, Li A. Fecal transplantation can alleviate tic severity in a Tourette syndrome mouse model by modulating intestinal flora and promoting serotonin secretion. Chin Med J (Engl). 2022;135:707–13.
36. Coban AY, Tanriverdi Cayci Y, Keleş Uludağ S, Durupinar B. Investigation of antibacterial activity of sertralin. Mikrobiyol Bul. 2009;43:651–6.
37. Ayaz M, Subhan F, Ahmed J, Khan AU, Ullah F, Ullah I, et al. Sertraline enhances the activity of antimicrobial agents against pathogens of clinical relevance. J Biol Res (Thessalon). 2015;22:4.
38. Zhong C, Fan QY, Li XJ. Analysis of 140 cases of adverse drug reaction to antipsychotic drug. J Qiqihar Univ Med. 2016;37:1537–9.
39. Bahr SM, Weidemann BJ, Castro AN, Walsh JW, deLeon O, Burnett CM, et al. Risperidone-induced weight gain is mediated through shifts in the gut microbiome and suppression of energy expenditure. EBioMedicine. 2015;2:1725–34.
40. Ait Chait Y, Mottawea W, Tompkins TA, Hammami R. Unravelling the antimicrobial action of antidepressants on gut commensal microbes. Sci Rep. 2020;10:17878.
41. Cussotto S, Clarke G, Dinan TG, Cryan JF. Psychotropic drugs and the microbiome. Mod Trends Psychiatry. 2021;32:113–33.
42. Bahr SM, Tyler BC, Wooldridge N, Butcher BD, Burns TL, Teesch LM, et al. Use of the second-generation antipsychotic, risperidone, and secondary weight gain are associated with an altered gut microbiota in children. Transl Psychiatry. 2015;5:e652.
43. Liu YW, Liu WH, Wu CC, Juan YC, Wu YC, Tsai HP, Wang S, Tsai YC. Psychotropic effects of Lactobacillus plantarum PS128 in early life-stressed and naïve adult mice. Brain Res. 2016;1631:1–12.
44. Liu WH, Chuang HL, Huang YT, Wu CC, Chou GT, Wang S, et al. Alteration of behavior and monoamine levels attributable to Lactobacillus plantarum PS128 in germ-free mice. Behav Brain Res. 2016;298:202–9.
45. Liao JF, Cheng YF, Li SW, Lee WT, Hsu CC, Wu CC, et al. Lactobacillus plantarum PS128 ameliorates 2,5-Dimethoxy-4-iodoamphetamine-induced tic-like behaviors via its influences on the microbiota-gut-brain-axis. Brain Res Bull. 2019;153:59–73.
46. Wang Y, Jing M, Hua Y, Hu X, Sun M. Clinical efficacy of Bifidobacterium triple viable powder as add-on therapy in children with tic disorder and its effect on the level of excitatory amino acids in serum. J Pract Med. 2022;38:212–6.
47. Yang J, Fu X, Liao X, Li Y. Effects of gut microbial-based treatments on gut microbiota, behavioral symptoms, and gastrointestinal symptoms in children with autism spectrum disorder: a systematic review. Psychiatry Res. 2020;293:113471.
48. Sun MF, Zhu YL, Zhou ZL, Jia XB, Xu YD, Yang Q, et al. Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: Gut microbiota, glial reaction and TLR4/TNF-α signaling pathway. Brain Behav Immun. 2018;70:48–60.
49. Mejía-Granados DM, Villasana-Salazar B, Lozano-García L, Cavalheiro EA, Striano P. Gut-microbiota-directed strategies to treat epilepsy: clinical and experimental evidence. Seizure. 2021;90:80–92.
50. Zhao H, Shi Y, Luo X, Peng L, Yang Y, Zou L. The effect of fecal microbiota transplantation on a child with tourette syndrome. Case Rep Med. 2017;2017:6165239.
51. Zhao HJ, Luo X, Shi YC, Li JF, Pan F, Ren RR, et al. The efficacy of fecal microbiota transplantation for children with tourette syndrome: a preliminary study. Front Psychiatry. 2020;11:554441.
52. Wang N, Wu X, Yang Q, Wang D, Wu Z, Wei Y, et al. Qinglong Zhidong decoction alleviated tourette syndrome in mice *via* modulating the level of neurotransmitters and the composition of gut microbiota. Front Pharmacol. 2022;13:819872.
53. Shui L, Yang X, Li J, Yi C, Sun Q, Zhu H. Gut Microbiome as a potential factor for modulating resistance to cancer immunotherapy. Front Immunol. 2020;10:2989.
54. Seeman MV. The gut microbiome and treatment-resistance in Schizophrenia. Psychiatr Q. 2020;91:127–36.
55. Holmes M, Flaminio Z, Vardhan M, Xu F, Li X, Devinsky O, Saxena D. Cross talk between drug-resistant epilepsy and the gut microbiome. Epilepsia. 2020;61:2619–28.