MICROBIOME: THE MISSING LINK IN NEUROPSYCHIATRIC DISORDERS

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ABSTRACT

The relationship between intestinal microbiota and the brain has been the focus of attention of the scientific world in recent years; >90% of the articles discussing the microbiome have been published only recently.[1] There is a strong and bidirectional relationship between the brain and the gut. Gut bacteria communicate with the intestinal epithelium and the immune system cells, with this communication causing many autoimmune, metabolic, and neuropsychiatric diseases. New horizons have been opened in the understanding and treatment of neuropsychiatry disorders. Microbiota dysbiosis can be restored with faecal microbiota transplantation, dietary arrangements, and probiotics. The efficacy of faecal microbiota transplantation in neuropsychiatric disorders is being investigated currently, and through the manipulation of the composition of intestinal bacteria in a conscious way, the treatment of neuropsychiatric disorders may be performed in a cheaper, easier, and natural way in the near future. Searching through the relevant literature on PubMed, EMBASE, and Google Scholar electronic databases, this is one of the first articles to discuss faecal microbiota transplantation in neuropsychiatric disorders in detail.

Keywords: Gut, microbiota, brain, psychiatry, faecal microbiota transplantation (FMT).

THE HISTORY OF THE MICROBIOME

The term 'microbiome' is used to denote all organisms living in the body and their genetic material; the term 'microbiota' is used to denote populations of micro-organisms in the different floras of the body (e.g. intestinal microbiota, vaginal microbiota).[1] A total of 380 trillion micro-organisms live in the gut. This number is >10-times the total number of human cells.[2] Furthermore, these micro-organisms contain approximately 150-times more genes than in the human genome.[3] Élie Metchnikoff was the first to realise the importance of the microbiome to human health, with the Nobel Prize in Physiology or Medicine 1908 awarded to Metchnikoff for his contribution to the understanding of cellular and humoral immunity.[4] Two years later, the first article concerning how probiotic bacteria can be used in the treatment of depression was published by Phillips.[5] However, interest in this subject only lasted for a short time. Throughout the following years, the relationship between intestinal microbiota and the brain was not studied.

Old Friends

The idea that micro-organisms may not all necessarily be harmful has been remembered again nearly 80 years after publication of Phillips' article. Strachan[6] has argued that there may be a relationship between hygiene (increased use of antibiotics, disinfectant cleaning products, modern lifestyle, and urbanisation) and the increase in the incidence of allergic diseases. Rook[7] has looked at the human-microbiota relationship from a broader perspective. He has argued that *Homo sapiens* have evolved along with 'the old friends' in the body, namely micro-organisms, for millions of years.[7]

The Leaky Gut

The surface of the intestinal mucosa is about 260–300 m^2 (almost the size of a tennis court).[8] More than 7,000 bacteria subspecies live in this vast area.[3] Intestinal bacteria produce active

metabolites (neurotrophins and antigens) that affect human cells.[9] The mucosa is in constant contact with bacteria and metabolites and the intestinal epithelium and mucus layer act as a physical barrier to bacteria and antigens.[10] If microbiota change because of the influence of alcohol and nutrition (dysbiosis), the intestinal epithelial wall will be destroyed; this causes increased epithelial permeability and 'leaky gut' occurs. Antigen bacterial metabolites leak into the bloodstream from the weak intestinal epithelium and an immune reaction occurs.[11] In addition to leaky gut, subepithelial dendritic cells produce exosome-containing bacterial material. Exosomes reach the brain through the blood and lymph.[12]

MICROBIOTA–GUT–BRAIN AXIS

Another method of interaction between bacteria and the human body is direct communication. Intestinal bacteria interact with the first step of the cytokine production pathway, the intestinal mucosal cells' toll-like receptors (TLRs). TLRs are also widely available in neurons.[13] Therefore, if the gastrointestinal system is referred to as the largest immune organ,[14] the intestinal microbiota is the forgotten organ.[15] The vagus nerve is another way of communicating between the gut and brain; any change in the gut is transmitted to the brain by the vagus nerve.[16] The possible mechanisms of the effect of the microbiota on the central nervous system are as follows:

- Microbiota dysbiosis[17]
- Antigen bacterial metabolites[10]
- Neuroactive bacterial metabolites (e.g. brain-derived neurotrophic factor, synaptophysin, postsynaptic density protein-95 [PSD-95])[18,19]
- Immune system activation[20]
- Vagus nerve-mediated effects[16,21,22]

Microbiota studies in neuropsychiatric disorders have revealed surprising results. It is useful to review these studies in detail.

Schizophrenia

Several studies on immune system problems in schizophrenia have been performed. The incidence of rheumatoid arthritis has been found to be low in patients with schizophrenia;[14] inflammatory cytokine interleukin (IL)-1 receptor antagonist levels in patients with schizophrenia are high, an occurrence thought to protect the patient from developing rheumatoid arthritis.[23]

It has been shown that anti-gliadin antibodies and gluten sensitivity are increased in patients with schizophrenia;[24] there is also a relationship between non-coeliac gluten sensitivity and diseases such as autism and schizophrenia.[25] Casein antibodies are increased in patients with schizophrenia and those positive for casein immunoglobulin G antibody have an 18% greater risk of schizophrenia (positive casein immunoglobulin G is a predictor for schizophrenia).[26]

Neuroinflammation is considered the starting point for pathogenesis of schizophrenia.[27] In germ-free (GF) mice, production of brain-derived neurotrophic factor and N-methyl-D-aspartate (NMDA) 2a decreases.[28] Changes in microbiota composition may cause NMDA dysfunction in schizophrenia.[29] Minocycline (a second-generation tetracycline) shows an antipsychotic-like effect in rats,[30] and is also effective in the treatment of negative symptoms of schizophrenia.[31] The positive effect of minocycline in the treatment of schizophrenia may happen through a change in the bacterial composition of the microbiota. In a study comparing serological immune markers between schizophrenia, bipolar disorder, and control groups, it was found that microbial products in the systemic circulation caused immune disorders in the schizophrenia group.[32] Through probiotic therapy, inflammation subsides in patients with chronic schizophrenia.[33]

An interesting experiment with olanzapine (an antipsychotic drug) has been performed. One of two groups of GF mice was given a high fat diet only and the other received olanzapine in addition. At the end of the experiment, no differences were detected in terms of weight gain between the two groups. Olanzapine-related weight gain was not realised due to the lack of intestinal bacteria. In the second phase of the experiment, it was found that olanzapine had an antibiotic-like effect on the bacterial flora.[34]

Anxiety and Depression

In patients with depression, a chronic and mild inflammation is found. The source of this inflammation may be the leaky gut.[35] The relation between the microbiota and mood has been investigated, mostly in animal experiments. *Campylobacter jejuni* given orally leads to anxiety-like behaviour in mice,[36] whereas *Bifidobacterium infantis* has reduced depressive symptoms in GF mice;[37] *B. infantis* is called a psychobiotic

because of its antidepressant effect.[38] Probiotic drugs include copious amounts of this bacterium.

The anxiety scores of rats given *Bifidobacteria longum* and *Lactobacillus helveticus* have been found to decrease,[39] while *Lactobacillus farciminis* decreases the hypothalamic–pituitary–adrenal axis response to stress in mice.[40] In an experiment by Bravo et al.,[41] the anxiety and depression scores of mice given *Lactobacillus rhamnosus* for 28 days decreased. In another experiment, anxiety-like behaviour declined after 21 days of *L. helveticus* usage. When the same implementation was performed in IL-10 (an immunoregulatory cytokine) knockout mice, anxiety levels did not change.[42] This finding shows the influence of the immune system on the gut–brain axis.

Probiotic bacteria increase IL-10 levels in GF mice;[43] in experimental animals given *Lactobacillus* GG, an increase in plasma IL-10 levels was found.[44] Antidepressants create an anti-inflammatory effect via IL-10[45] and treat depression by acting on monoamines and the immune system. In a double-blind placebo-controlled study with healthy volunteers, the first group was given *B. longum* and *L. helveticus* R0052, and the other group received a placebo; urinary-free cortisol levels and anxiety/depression scores decreased in subjects who received probiotic bacteria.[46] The positive effects of probiotics in emotional tasks have also been shown through functional magnetic resonance imaging (MRI).[47] Microbiota may additionally play a key role in linking an unhealthy diet and depression.[48]

Autism

Autism is one of the diseases where the gut–brain axis is mostly studied.[49] In autistic mice, increased neuroinflammatory markers have been found,[50] while in another experiment, autistic behaviours returned with *Bacteroides fragilis*; this bacterium has been shown to repair intestinal permeability disorder through cytokine production and tight junction expression. Also, 4-ethylphenyl sulphate (a bacterial metabolite) has been found to result in elevated serum levels in autistic mice. When this metabolite has been given to normal rats, the emergence of autistic behaviours has been observed.[51,52] In autistic children, decreased *Bifidobacterium* species, increased *Lactobacillus* species,[53] and increased *Bacteroides* species[54] have been found. It has also been argued that a high carbohydrate diet increases the production of short-chain fatty acids in the gut, and their release into the systemic circulation leads to autistic behaviour.[55]

Alcohol Addiction

By weakening the wall of the intestinal mucosa, alcohol eases the release of bacterial antigens into the systemic circulation. These substances induce the secretion of proinflammatory cytokines (IL-1β, IL-8, and IL-18) by binding to TLR-4 and TLR-2 receptors of mononuclear cells in peripheral blood. Few studies have investigated links between microbiota and alcohol abuse, although in a study by Leclercq et al.,[56] 63 alcohol addicts were investigated. It was found that chronic alcohol consumption increased the levels of IL by activating inflammatory processes. A correlation was found between IL levels and the levels of alcohol consumption and craving.[56] In a second study by the same investigators, the role of intestinal permeability in alcohol addiction was examined. Intestinal permeability was found to be commensurate with the severity of alcohol dependence.[57]

REGULATION OF INTESTINAL MICROBIOTA

There are several ways to treat intestinal microbiota dysbiosis. These are prebiotic drugs, probiotic drugs, activated charcoal, and faecal microbiota transplantation.[9,58] A prebiotic enables an intestinal bacterium to become more dominant than other ones. A probiotic gets a special kind of bacteria into the body orally or rectally.[1] In a single year, >$1 billion is spent on probiotic drugs in the USA.[59] Activated charcoal is used in the treatment of poisoning that occurs after usage of high-dose medication as it prevents absorption from the intestines by binding to toxins. Tablets and capsules are used in reducing complaints of diarrhoea, indigestion, and bloating; these may help to relieve the gastrointestinal system and neuropsychiatric symptoms by binding to toxins secreted by microbiota.[9]

FAECAL MICROBIOTA TRANSPLANTATION: A RISING STAR IN NEUROPSYCHIATRIC DISORDERS

Stool was used for the first time for treatment purposes in China in the 4th Century,[60] and has been applied orally under the name of 'golden syrup' or 'yellow soup' in the treatment of diarrhoea.[58]

Interestingly, this technique was forgotten over the centuries and was recalled in 1958. Eiseman et al.[61] treated a pseudomembranous enterocolitis case with antibiotic-associated severe diarrhoea through faecal microbiota transplantation (FMT), however nowadays, a very high percentage of publications on FMT are regarding *Clostridium difficile* infection (*CDI*) and its treatment. This method has started to be used in the treatment of neuropsychiatric disorders in recent years.[58]

Preparation and Usage of Faecal Microbiota Transplantation

It is recommended to provide faecal material from a stool bank for transfer.[62] If this is not possible, health screening of a donor candidate should be performed.[63] The stool should be ≥150 g and fresh.[63] The receiver should be given a mild laxative a night before the application and the transplanted stool should stay for ≥4 hours within the patient's gut. An antidiarrhoeal drug (loperamide) should be given an hour before FMT.[58] The preparation of the stool material is as follows: the stool is diluted with water, milk, or saline and it is then mixed with a blender. This stool suspension is filtered with a filter or gauze to separate solid particles and the faecal suspension taken up into syringes.[63,64] The stool suspension can be sent to the duodenum through oesophagogastroduodenoscopy and can be applied to the colon through a colonoscopy or enema.[63] In three-quarters of cases, colonoscopy or enema has been used. In one-quarter of cases endoscopy has been used.[65]

Faecal Microbiota Transplantation in Neuropsychiatric Disorders

Information on the application of FMT in major psychiatric disorders is insufficient. In the following neuropsychiatric disorders, the effectiveness of FMT has been examined.

FMT can be an effective therapeutic technique for irritable bowel syndrome,[66] with the remission rates of irritable bowel syndrome case series ranging from 36–89%.[58] The neurological complaints of three multiple sclerosis patients have disappeared after FMT, and their quality of life has improved.[67] It has been reported that autistic children have benefited from FMT and their symptoms have regressed.[65] Any Parkinson's disease cases treated with FMT have not been reported yet. However, the chronic constipation of a patient with Parkinson's disease has been treated with antibiotic treatment; the patient's neurological symptoms completely disappeared after antibiotherapy.[68]

FMT is a reliable, easy, and cost-effective treatment[69] and its side effects are usually mild. In some cases, diarrhoea presented a day after FMT application, and only a few cases have reported constipation, gas, and abdominal discomfort.[63] In a recently published comprehensive review article, the serious side effect rate was determined to be 2%.[70] In this study, FMT was applied to all cases of *CDI*. In *CDI* cases, serious side effects such as infection, sepsis, and bowel perforation are more likely to occur, therefore this study does not reflect the neuropsychiatric sample. It can be said that FMT is a much more reliable treatment in cases with a neuropsychiatric disorder however the information obtained from the neuropsychiatric patient sample is composed of a small literary anthology (there were not any randomised controlled trials included). There is a need for more evidence and testing in terms of the effectiveness and reliability of FMT.

FMT is often viewed as an undesirable treatment,[64] therefore, some patients respond negatively. Women and young people are more reluctant than men and the elderly to try FMT and 33% of patients are unwilling to pay for FMT.[71] As an alternative to FMT, oral capsule treatment has been tried. After centrifuging and placing the stool in swallowable capsules, it is frozen at -80°C. Fifteen frozen capsules per day are taken orally.[72]

CONCLUSIONS

The impact of bacteria that live in the intestines on human health and especially on neuropsychiatric functions has been the centre of interest in the scientific world over the past 5 years. Studies on the microbiome–brain axis comprise mainly GF mouse experiments and due to the large number of bacteria in the human intestinal microbiota, it is difficult to carry out randomised controlled trials. Scientists uncover new treasures from this 'gold mine' every day. The beneficial effects of probiotics have been shown many times in experiments with mice however any positive effect of the probiotic bacteria *L. rhamnosus* on psychological parameters in healthy volunteers has not been found.[73] The micro-organism-immune system–diet–brain relationship will be revealed gradually and in the near future, psychomicrobiotics will be used in the treatment

of neuropsychiatric disorders. Additionally, FMT, being a cheap, easy, and reliable treatment method will be used commonly. The gut–brain axis seems to be the missing link that will provide a full understanding for the treatment of neuropsychiatric disorders.

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