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Chapter

The Interaction of Gut Microbiota-brain Axis in Relation to Human Health with the Use of Animal Models

Gaythri Thergarajan and Subha Bhassu

Abstract

The human gastrointestinal tract harbors an extremely complex and dynamic microbial community, including archaea, bacteria, viruses and eukaryota. This gut microbiota usually works with the host to promote health but can sometimes initiate or promote disease. Dysbiosis relationship in gut health indicating the role gut microbiota in promoting the development and progression of brain health. The human gut microbiota is a complex and dynamics microbial community that plays an important role in protecting the host against pathogenic microbes, modulating immunity and regulating metabolic processes. The insights can be elucidated with help of latest omics technology and animal model studies.

Keywords: gut microbiota-brain axis, human health, animal models

1. Introduction

The gut microbiome has been widely accepted to be one of the vital factors causing various disease in human. This area of research has become the niche for many scientists from various fields to explore. Most of the research works are focused on elucidating the influence of gut microbiota in the brain development [1]. Diet plays a crucial role in altering the gut microbiota and some studies focuses on understanding how diet alters gut microbiota and its effect on the development or prevention of metabolic, cardiovascular and brain diseases [2]. Animal studies have always been an important tool in the biomedical research. The interactions of the gut microbiota-brain axis have been studied using various animal models. However, most of the animal research has only able to reveal the fundamental theory such as the diversity of microbial community, the potential microbial pathways and the dysbiosis of the gut microbiota due to diet and drug [3]. The inability of translating many great findings into human system is withdrawal point of animal work [3]. Later, the advancement in the omics-technology has pave the way in the identification of metabolic pathways, microbial species, and metabolites that have strong association with the progression and cure of diseases. Here we have reviewed the interaction of the gut microbiota and
brain axis, the pathways, and how the gut wealth affect the human health. Researches on microbiome is translatable into treatments that is able to alter the gut microbiome which could transform the common diseases. This paper also reviewed how the animal research and the application of omics technologies has contribute towards inventions of therapies.

2. The bidirectional communication in microbiota-brain axis

Researches on gut microbiota-brain communication focused on its effects towards digestive functions. However, the current interest in microbiology and neuroscience has given way to understand the psychophysiological consequences of gut-brain or brain-gut as a two-way network [3, 4].

The gut microbiota-brain axis is the term referring to the two-way communication between the gut and the brain [5–8]. More importance is given to elucidate the function of microbes in the gut microbiota-brain axis link as the microbiota can be altered intentionally. The exact mechanism of communication between the gut microbiota and brain has yet to be elucidated, however, the multiple pathways have been identified. The gut microbiota possibly causing an effect on the brain function through the nervous system, endocrine system, immune system, and metabolic system [8].

The bidirectional communication is important in analysing the gut-brain signalling pathways which regulate the host brain and behavior [8]. This bidirectional communication pathway is consisting of the central, enteric, and autonomic nervous systems and the hypothalamic-pituitary-adrenal (HPA) axis. These pathways use the metabolites and the by-products of gut microbes as a communication factor [9]. In recent time, active researches on gut microbiota-brain axis targets the main pathways of the vagus nerve system, the immune system, the neuroendocrine systems, the neurotransmitters and the metabolites [10]. The vagus nerve is responsible in making a physical connection of the gut-brain combo, whereby it allows the brain to sense the gut environment. The vagus nerve extends from the brain to the gut, carrying motor signals and controls the internal digestive, heart and respiratory rate. These motor signals are also transferred to the intestinal cells causing an effect on the gut microbiota [11, 12].

Next, the connection between the gut microbiota and the host immune system is another key research area as studies showing inflammation in neurological and metabolic related disorders [13–16]. The development of low-grade systemic inflammation is associated with impairment in immune response and dysbiotic microbiota. The dysbiosis can regulate on both the innate and adaptive immunity and cause an effect on the gastrointestinal tract and throughout the body. This has been clearly proven in autism spectrum disorders (ASD), epilepsy, Alzheimer’s disease, Parkinson’s disease and cerebrovascular diseases [16].

Recent findings have showed that the gut microbiota triggers the HPA axis. This pathway controls the neuroendocrine system that modulate stress response, mood and emotions [17]. Evidences shown that microbiota controls the gut hormones and then later regulates the hormone responsible for stress, mood and emotions [17–19]. Gut hormones proven to involve in the physiological processes causing anxiety and depression [18]. A disruption in this bidirectional pathway has been linked with depression, irritable bowel syndrome (IBD) [19] and obesity [18]. These evidences clearly show that gut hormones are potentially regulating the well-being of the host.
The gut microbiota on the other hand, has a major function in the metabolic pathway, which involves energy homeostasis and metabolite production. Animal studies have shown evidence on the ability to produce and metabolise a range of neurotransmitters [1]. A number of neurotransmitters which function as hormones including dopamine, serotonin, noradrenaline, gamma-aminobutyric acid (GABA) has been identified in the context of gut microbiota and brain axis network. These are also known as the hormone-like neurotransmitters which are not only produced in the gut but they do play role in the microbiota. Various factors such as diet, drug, or disease can potentially change the composition of gut microbiota and at instant alters the hormones [20]. In the context of diet, the composition and activity of the gut microbiota can be majorly affected due to the type of food consumed by the host [20].

3. Gut microbiota affecting human health

The alterations of the gut microbiota have the potential to affect the human health and causes various common health as well as major disorders. Firstly, studies have shown the link between the gut microbial community with the common metabolic diseases including obesity, type-2 diabetes, non-alcoholic liver disease, cardio-metabolic disease, and malnutrition [21]. This study has attempted to reveal the connection between abnormal gut microbiota composition and it by products to the dysmetabolism in the diseases mentioned earlier.

The number of cases related to obesity has increased tremendously in the developed countries over the past years [22]. Individuals with obesity has been reported with low microbial gene richness with a relative increase in adiposity, resistance towards insulin, and inflammation [23]. The use of antibiotics before and during pregnancy or in childhood may cause a receding microbial richness of infant and children, increasing the chances of acquiring early-onset of obesity [24, 25]. It was not proven that the receding microbial community is the primary causal factor of obesity, however, it has been shown that low microbial gene richness could be improved with dietary interventions [26].

Type 2 diabetes (T2D) and prediabetes have potential link with altered gut microbiota. An epidemiological study comparing individual without colectomy and patients with total colectomy showed a higher risk of acquiring T2D [27]. This disease has been showing an increased prevalence, especially targeting the adult population and leading to endocrine disorders [28]. Studies have been targeting the products of gut microbiota which may involve in elevating the glucose level in blood. In another study, the gut microbiota of prediabetes individuals shown that there is a reduction in number of Akkermansia muciniphila and increase in the number of bacteria pro-inflammatory potentials [29, 30]. A. muciniphila is a butyrate-producing bacterium, the reduction on its abundance in the gut may lead to aggravation of opportunistic pathogens [31, 32]. The challenge in revealing the significance of altered gut microbiome to T2D is that the patients are heavily medicated where that would be another main factor causing a dysbiosis to the gut microbiome. That is the reason for using prediabetes individuals as the drug-naïve targets [29].

The gut microbial dysbiosis can also be linked to cardio-metabolic diseases (CMD). Study [33] reported an increase level of Enterobacteriaceae and oral cavity species in the gut microbiota of individuals with CMD compared to healthy controls. The microbiota of these individuals has reduced Bacteriodes spp. and anti-inflammatory species. In another report, a dysbiotic gut shows potential link to
ischaemic heart failure with an elevated level of genes responsible in the synthesis of Lipopolysaccharides [34]. This shows that a disruption in the gut microbiome leads to heightened fatty tissues in the host. A sequencing study done by [35] showed a link between microbiota and atherosclerosis, and later, trimethylamine N-oxide (TMAO), a metabolite from the gut microbiome found to be the causal link to CMD [36].

The microbiota-brain interaction clearly shown is effects on the progression of brain disorders. The development of Parkinson's disease has been linked with formation of protein misfolds in alpha synuclein caused by *Escherichia coli*. *E. coli* was found to produce curli, a protein which causes misfold in other proteins and this error is transmitted to the brain via the vagus nerve [37]. The onset of the ASD has been suggested to cause by segmented filamentous bacteria in the gut. Occurrence of infection during pregnancy causes the bacteria to trigger the T-helper cells to produce immune molecules which later travels to the fetus's brain and provoke autism like behaviors [20].

4. Animal models of gut microbiota research

Intense animal research is intended to gain insight into understanding the reason why there are obvious differences in the human gut microbiota acquired by the healthy and unhealthy individuals. Although the context of the gut microbiota and brain axis is new, it has been well acknowledged in recent time. It is known that gut microbiota regulates the gut metabolism, and various animal studies have revealed that gut microbiota majorly affects the host immune system as well [38]. A number of animal models have been very crucial in enhancing the understanding towards the gut microbiota-brain axis relationship. Yet there are some disadvantages of using the same method.

First of all, the mouse model which would be the common animal model as it can be a good control for age, gender, diet and treatment factors [3, 39–41]. A study uses the *Lactobacillus rhamnosus* to cause region-dependent alterations in the mouse brain, showed neurochemical and behavioral effects [39]. An alteration in the GABA (γ-aminobutyric acid), the main neurotransmitter of the central nervous system was witness, causing an implication on the pathogenesis of anxiety and depression. However, in the vagotomized mice, the effect was not found, indicating the vagus pathway to be the major pathway between the gut and the brain [39]. In this study the vagotomized mouse model being used well to identify the role of bidirectional pathways. Genetic mouse models are also available to target gene specific manipulation. Many studies using mouse model have revealed the influences on the neuro-physiology and behavior, cognition, anxiety and depression related issues. However, the translation of research finding using a mouse model on human is difficult. This is very similar to rat model as well. Studies which target the link between gut microbiota and stress uses hamster model [42, 43]. Hamsters on the other hand are difficult to evaluate as they always live in isolation, which allow them to develop metabolic disorders.

Other than mammals, there are also non-mammalian models such as zebrafish [44–47] and *Caenorhabditis elegans* [48, 49]. *C. elegans* has a specialized microbiome is abundance with bacterial taxa where the presence and the number of bacterial taxa found in each individual worm vary from each other. So, the real challenge of working with this organism is to determine the stability and the connection of its microbial community with the host [48]. Many studies revealed the interaction between the
microbiota the host can be achieved by using *C. elegans* as a model organism. In another research paper [50], the effects of host environments on bacterial gene expression was successfully studies using the tractable genetic model, *C. elegans*. In this study, the *E. coli* grown *in vitro* were fed to the host, revealed that the host genetics alters the metabolic pathways of the host. The availability of genetic manipulation is the best feature of *C. elegans* model as this could complement the analysis of individual bacterial taxa. A forward and reverse (two-sided) genetic analysis allows the possibility to characterize the microbial processes and its interaction between the host [48].

Zebrafish on the other hand, has been a well establish model animal in the biomedical research, yet the use of this organism in the gut microbiota research has only happened recently. The sequencing method using the bacterial 16s RNA genes revealed the microbial community comprising the bacterial phylum Proteobacteria, Firmicutes and Fusobacteria at all the life cycle stages of zebrafish [44]. Recent studies, have manage to understand the link between the host, microbes and immune response. It has been suggested that gene editing technology may work by targeting a specific gene-deficient in zebrafish to enhance the understanding of immune responses [51]. This animal can be useful in elucidating the conserved molecular mechanisms as they possess similar gene expression and regulation even with different when the organism is isolated from different environment and having varying physiology [51].

<table>
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<tr>
<th>Animal</th>
<th>Influence on brain and behavior</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Mouse</td>
<td>Influences the neurophysiology and behavior such as cognition, anxiety and depression</td>
<td>Translation difficulties on human</td>
</tr>
<tr>
<td>Rat</td>
<td>Influences the neurophysiology and behavior such as cognition, anxiety and depression</td>
<td>Live in isolation and develop metabolic disorders</td>
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<tr>
<td><em>C. elegans</em></td>
<td>Non-mammalian model for validation Tractable genetic model, allow analysis on genetic manipulation</td>
<td>Translation difficulties on human is very high</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>Non-mammalian model for validation Reveals the immune response of host Good model for genetic analysis</td>
<td>Translation difficulties on human is very high</td>
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*This table summarizes animal models used in gut microbiota-brain axis research.*

5. Omics in microbiota

The advancement in understanding the interaction between gut microbial community and its host is only possible with recent microbial genomics. The main omics techniques, including metagenomics, metataxonomics, metatranscriptomics, and metabolomics allows the exploration of this area of research. At the initial stages of research, bacterial gene analysis was allow relying on the 16S rRNA sequencing method. Scientists were targeting the conserved region of the nucleotide sequence and compared that with other reference sequences to identify the type of bacterial species in the gut [52, 53]. However, sequencing with 16S provides less information about the functional microbial community in the gut which did not allow the studies to make a correlation between microbes and its potential effects causing failures in experiments [53]. This method was mostly targeting the gut bacterial community but not the other type of microbes such as archea and viruses.
Later, the sequencing method was complemented by the metagenomics approach, where the whole genomic content was accessed using the microbial DNA. Reference genes were used to compare the similarities against the newly available genomic data to identify the functions of the genes coding for the new microbial community [54]. This approach could provide important information on all types of microorganism including archaea, fungi, and viruses at their strain level [55, 56]. However, this approach was not sufficient to understand the functional microbial community at the DNA level, it was needed to translate into functional proteins. Thus, metagenomics was accompanied by metatranscriptomic analysis by translating microbial DNA into RNA [57]. The RNA was later translated into proteins and analysis on microbial functions was continued using metaproteomics. This approach was found to be more comprehensive as it could differentiate between metabolically active microbes in the gut [58]. Mass spectrometry is being used in metaproteomics to measure the expressed proteins which is the important for most biological processes. This information is vital when studying the *in vivo* host-associated microbiomes interactions [57].

In addition, to shed light on the identification of microbial activities in dense, microbial metabolites were targeted by using a tool known as metabolomics. Metabolomic uses techniques such as nuclear magnetic resonance (NMR) spectroscopy or mass spectroscopy (MS) to measure the metabolites present in the gut. Studies has shown that MS is more sensitive in identification of metabolites compared to NMR [59]. The metabolites act as the signaling markers in the communication between the host and its microbiome. As such, imbalance in the intestinal metabolites can be a factor towards development of disease in the host [60]. The various omics technologies explained earlier has been summarized in Figure 1.

In the presence of all these omics technologies, scientist believe that they could identify the correlation of microbiome with important human diseases. The gut microbiome influences health, due to the interactions with the immune system.

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*Figure 1.* The use of various omics technologies in revealing the gut microbiota and brain axis relationship.
Understanding the microbial signals will allow new ways to tackle disease. But it is not as easy as it sounds, where more than 50% of the human gut microbiome is yet to be elucidated.

6. Future directions: therapeutic interventions

It is important to identify the key gaps and needs in gut microbiota-brain axis research to plan the future directions and therapeutic interventions. Scientists are only beginning to understand the network between gut microbiota-brain axis. Unraveling the modulation of gut microbiota on the brain health, increases the potential for improving the quality of human life and well-being. The gut microbiome responses to the external factors such as diet and drugs. Drugs are able to modulate the gut microbiome. An integrated understanding on the interaction between the drugs and gut microbiome using the meta-omics technologies can be a major approach towards drug treatment and usage of drugs on certain diseases. There should be rapidly growing studies towards the drug-microbiome interactions targeting available drugs in the markets [61].

Most studies in this field has only attempted using animal models. This method is time consuming, expensive and the findings are difficult to be translated on the human subjects. Culturing the human microbiome by ex vivo culturing together with the meta-omics approach allows development microbiome assays for rapid testing on drug microbiome interactions [57]. Future studies should be focused on understanding the immunological effects of human gut microbes and their role in brain disorders, mapping of neurotransmitters produced by gut microbiota and effect of microbes in early brain development by using human subjects [9]. These interventions are focused in providing nutritional and therapeutic strategies and likely to improve the human quality of life. In most cases when it comes to brain disorders, it is unlikely that these finding provide a permanent cure, however by having the knowledge of these bidirectional communication between the gut microbiota and the brain axis, early predictions or strategies in altering the microbiome to slow down the process would be definitely possible [9].

Nutritional strategies can also be another great practice and are even already on the market, including foods and supplements which help to improve mood, sleep and stress. For instance, altering the diet plan for a child with ASD, could influence the gut microbiota in providing a comfort to gastrointestinal irritation and calm anxiety and hyperactivity. It could be even possible to use probiotics as a complement to drug and therapy for disorders such as schizophrenia. So far many successful trials have achieved by showing the efficacy of probiotics in both strain-specific and disease-specific clinical cases [62]. Studies showed that probiotic supplements are able to benefit the host by producing high bacterial count and the antibiotic therapy could cause a reestablishment of the host microbiome [63, 64].

7. Conclusions

Many advance technologies and animal studies have revealed many interesting facts in elucidating the communication between the gut microbiota and brain axis. However, the fact that most of the studies failed to show the translation of their research finding into human subject is the major gap to be filled in area of research.
Effect of Microbiota on Health and Disease

Thus, future direction of gut microbiota-brain axis research should focus on the mapping of human gut microbes and their byproducts and finding the immunological effects on the brain disorders. There should be more intervention and preclinical studies focusing on human subjects. The direct link between the human gut microbiota and brain can be only achieved if the bidirectional pathways are revealed from researches focusing on human population.

Acknowledgements

We would like to acknowledge the TRGS grant entitled TR001B-2018A awarded by Ministry of Higher Education. (MOHE) to Prof Suresh as the Program Leader for TRGS and we duly acknowledge to his leadership for this project.

Conflict of interest

The authors declare no conflict of interest.

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