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Effects of Gut Microbiome on Brain Development: A Review

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تأثيرات ميكروبيوم الأمعاء على نمو الدماغ: مراجعة

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ABSTRACT

Microbiome is an enormous abundance and diversity of microbial community that lives symbiotically in and on the human body. They offer important and beneficial functions for the human health. Most of microbiome lives in the in gut and participate in the regulation of body physiology. Recently the importance role of the microbiome in the regulation many physiological aspect has more attractive. Moreover, it was found that the absence of gut microbes caused immune and metabolic alteration in the experimental animal, as well as developing number of infectious diseases due to disturbance of microbial community composition. Interestingly there is an evidence that commensal microbiome can influences the brain development, cognition and behaviour via gut-brain axis. Furthermore, it was observed that changing in the behaviour can lead to the alteration in the composition of intestinal microbial community and vice versa the alteration in the commensal gut microbiota composition can cause depression like behaviour. The gut microbiota's function in brain development will be covered in the review. The understanding of interaction mechanisms between gut microbiota and brain development offer new approach to treat various mental diseases. The conclusions, there is a requirement for applying microbiome analysis on broad human community along life-course with more respect to individual differences between people, and for further development of analytical approaches

Keywords: mental diseases; brain development; gut microbiome; gut-brain axis

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INTRODUCTION

Microbiome is a multitude of microbes such as viruses, bacteria and fungi that lives in a symbiosis relationship with human. They inhabit in all the internal and external surface of the human body. Many evidences confirm the essential role of microbiome for the human health and diseases. More than one hundred trillion of these organism's exhibit in the human gut [1]. These commensal gut microbes produce thousands of metabolites that essential for human health and maintaining homeostasis. The disruption in the composition community of gut microbiota can involve in the development of metabolic diseases [2,3] and mental disorders. There is evidence that there is interaction between gut microbiota and central nervous system [4]. Also some evidences indicated that there is an association between dysregulation of the gut microbiota and neurological and psychiatric disorders [5]. Therefore, various effort were introduced to reshaping the gut microbiome composition such as using of probiotic in the first decade of the twentieth century for improving mental health or treating psychiatric disorders [6].

Moreover, various studies on animals showed that responding to the stress, anxiety, depression, social behaviour and communication can be affected by gut microbiota. The most convinced observation built on transferred behavioural traits between mouse strains via swapping their gut microbiota. Furthermore, it was observed that anxiety and depressive-like behaviours was induced in the rodents colonized with the gut microbiota of humans suffering from the these symptoms [7] Interestingly it was also found, in the past decade, that there is an interaction between the gut microbiome and the central nervous system [4]. This could be developed a new way for treating some nervous situation like autism [7].

This review will come to insight the light on the way that microbiome interacts with brain and the role of gut microbiome in regulating the neurological function and brain development.

WAY OF INTERACTION BETWEEN BRAIN AND GUT MICROBIOTA

Gut microbiome interact with brain via bidirectional signalling way called gut microbiome –brain axis. This way connects between gastrointestinal tract and brain. This connection is very important to maintain homeostasis and regulate the nervous systems (even central or enteric), hormonal and immunological levels [8]. Disturbance of these systems can alter stress response and all our behaviour. The importance evidence of this bidirectional connection is the association of between psychiatric symptoms of stress like anxiety and diseases of gastrointestinal tract such as irritable bowel disorder (IBS) and inflammatory bowel disorder (IBD) [9]. In addition, association of several nervous conditions such as such as autism, depression and schizophrenia with gut microbiome composition is another evidence of gut-brain-axis. Interestingly the brain-gut communication is highly affected by gut microbiome which leading to the presences of gut microbiome-brain axis term. However, there are some individual differences due to individual variability of gut microbiota composition and abundances of some bacteria [8].

Gut microbiota can interact with brain via several mechanisms such as neural, immune and endocrine pathways [5]. A variety of neuroactive chemicals modulated neurotransmitter levels are produced by gut microbes such as γ-aminobutyric acid (GABA) that produced by

Bacteroides bacterial genus. Recently, it was observed that brain depression symptoms associate with increasing Bacteroides levels, which suggests that (GABA) produced by this bacterial species may involve in the gut –brain axis. Neurotransmitters imbalances, inflammation or over activation hypothalamus–pituitary–adrenal axis might be resulted from microbial dysbiosis in the gut [7]. However, the mechanisms of communication is unclear exactly and most of research studied the effects of alteration of neuronal signals from brain to the intestine [9]. Understanding the role of gut microbiota in mental function require to know the effect of microbiome on neurological function and brain development.

THE ROLE OF MICROBIOME IN THE REGULATION OF NEUROLOGICAL FUNCTION

The brain communicates with the gut through brain-gut axis that formed from bidirectional network. This network responsible for monitoring and integrating the gut function and link them with nervous system (central, autonomic, enteric, neuroendocrine, enteroendocrine and neuroimmune systems). This axis mediates genetic and environmental factors that affect the brain function and development, also it was involved in psychiatric disorders [5]. The term microbiome-gut-brain axis was suggested to indicate the role of gut microbiome in the development and function of the nervous system, via influencing the gut –brain-axis [9]. Interestingly, the ability of changing microbiome by different environmental factors such as diet [10], antibiotic, sleeping behaviour provide new approach to treat psychopathologies. The effect of antibiotic on gut microbiome composition was well obvious from the psychiatric side effects of antibiotics ranging from anxiety to depression. It was found that a transient alteration in the composition of commensal microbial community in the gut in adult mice and increasing in the exploring behaviour and hippocampal expression of brain-derived neurotrophic factor occurred due to administer of non-absorbable antimicrobials orally [5].

Diet is another factor influence the shaping and diversity of gut microbiome consequently linked with psycho pathological outcomes. It was observed that alteration of microbial diversity and reduction in the synaptic plasticity [11] and more vulnerable to anxiety-like behaviour in mice [5] associate with consuming of high fat diet (HFD). Moreover, significant impairment of a spatial bias development for long and short-term memory and reversal training associate with alteration microbial diversity due to consumption of high carbohydrate diet in mice [12]. In contrast neuron growth and increasing in the level of brain derived neurotrophic factor as well as improving cognition was observed with consumption low calories diet in adulthood mice [13]. Generally, improvement the cognitive ability associates with diet that increases the diversity of gut microbiota [5].

Diet and antibiotic are the main factors that affect the brain functions via shaping the diversity of microbiome. However, alcohol consumption, [14] smoking and life style, have can influence microbiota composition [5].

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INTERACTION BETWEEN GUT MICROBIOME AND BRAIN DEVELOPMENT

Because of brain development start from embryonic period and continue to the post adolescence period microbiome composition, environment, genetic can affect neurodevelopment along this time. During pregnant period, the link between the neonatal and the external environment is the mother's metabolism and immunity. Therefore, neural disorder such as anxiety, autism, attention deficit hyperactivity disorder, depression and schizophrenia can be occur due to different factors threat maternal homeostasis such as infection, poor nutrition or prenatal stress [15]. External stressors affect fetal development via maternal microbiome which could be altered the development signals or produced in appropriate stimuli of development. Indeed, the connection between maternal microbiome and altering neuronal development and the psychopathologies is still not well understood due to involving multiple interaction system. For example, in addition to affecting multiple microbiome dependent and independent immunoregulatory pathways such as metabolic [16] and neuroendocrine [17] systems and associated dysbiosis of the high fat diet, consumption of this diet type during pregnancy can cause behavioural disorder later. However, its effects and outcome depends on developmental stage at which the disorder occurs [18,19].

Disruption the gut microbiome regulating role in the immunity causing an inflammation in the mother appears to be one of the important mechanisms contributed to abnormal neurodevelopment. For example increasing circulating cytokines levels during pregnancy showed negative impacts on neural development [17] and could act by altering the fetal immune environment [20].

Dysregulation of immunity can be resulted from gut microbiome disruption. Microbial disturbance occurs via various such as food, antibiotics leading to inhibition of microbial metabolites such as short chain fatty acids (SCFAs) that regulate immune system as well as supressing of interaction between microflora and Toll-like receptor (TL-R) and T-cell [21]. Moreover, induction of pro-inflammatory bacterial metabolites occurs due to imbalance of gut microbes resulted from consumption of high fat diet [5]. In addition, disruption of gut microbiota can affect the activation of spinal nerve pathway consequently CNS influenced [22]. This confirmed via observation that disruption of gut microbiota due to exposure to repeated stress associate with decreasing the levels of pro-inflammatory cytokines [5]. In addition to the effects of stress on fetal development, exposure to the stress also lead to changes in the maternal gut microbiome via alteration in the maternal hypothalamus-pituitary- adrenal axis [23]. This dysbiosis have further adverse effects on the hypothalamic-pituitary-adrenal (HPA) axis via alteration tryptophan metabolism and other dysbiosis correlated pathways [5].

Moreover, the biosynthesis of circulating 5-hydroxytryptamine (5-HT), which acts on regulation of division, differentiation and synaptogenesis of fetal neuronal cell [24], is regulated by maternal gut microflora. Therefore, changing in the microbiome can change the level of (5-HT) consequently alteration in the brain development is resulted [5]. Maternal gut microbial changes could be also influenced the formation of blood–brain barrier (BBB), which is an important component to development of central nervous system (CNS), neuronal growth and specificity [25].

As the gut microbiome can affect the brain development during pregnancy period, it can affect the neuronal development after birth as well. Therefore, disruption microbiome composition can influence mental health and brain development via immune interactions and gut-brain axis. It was observed that absence of gut microbiome associates with increasing motor activity and anxiety reduction in mice [26], in addition to elevation of hormone and corticosterone of plasma adrenocorticotropic and reduction levels of brain-derived neurotrophic factor (BDNF) in the cortex and hippocampus [5].

Also it was found that microbiome play an important role in presenting of normal social behaviours, regulation of repeated behaviours, developing of non-spatial memory, and pain signalling development. It is important to note that the absence of developing appropriate microbial signals in early-life can result in irreversible abnormal mental development even with later exposure to microbiome [5].

Effects of Microbiome on immune system either directly, via activation of the vagus nerve [27] consequently stimulation of bidirectional connection with CNS, or indirectly via impact innate immunity resulted changing in the levels of circulated cytokines, represent the most important mechanism to affect brain development.

Microbial metabolite such as SCFAs and various bacterial compounds play an important role in the regulation of gut–brain axis, local immunity and systemic immunity. For example, microbial SCFAs stimulate G protein receptors (GP-R) that facilitated their interaction with nerve cell. Moreover, SCFAs involved in the development modulation of the brain and behaviour, as well as autism development implication [5] via their ability to cross BBB barrier, regulation the homoeostasis of microglia and releasing of gut peptides from enteroendocrine cells [28], regulation the synthesis of gut-derived 5-HT from Enterochromaffin (EC) cells [7].

In addition, dopamine [5] γ-aminobutyric acid [7] histamine and acetylcholine are immunoregulatory and neuroactive compounds produced by gut microbes [5].

Another way that microbiome regulate brain function is affecting the metabolism and availability of amino acid tryptophan, which necessary for synthesis of serotonin in the CNS [29]. It was observed that reduction of tryptophan concentration affect mood and cause represent of depression symptoms in the patients that responded to the inhibitors of serotonin reabsorption [5].

Moreover, regulation of gut peptides releasing from the enteroendocrine cells, that affect gut–brain hormonal communication [5] and microglia homoeostasis regulation, represent another way for influencing brain function by gut microbiome [30].

It was mentioned that microbiota–gut–brain axis working in bidirectional ways to regulate behaviour like depression. It was observed that there is an alteration in the microbiome composition resulted from decreasing the function of inflammasome, or using of pharmacological treatments due to behaviour changes by high stress levels [31]. Moreover other study found three finding first, there is an association between reduction the time of immobility during obligated swimming and the absence of gut microbiome in free germ mice compared with control normal mice; Second, there is a significant differences between the composition of gut microbes in the clinical sample of healthy mice and patient mice with major depression disorder; third in germ free mice, depression-like behaviours resulted from

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transplantation of gut microbiome from Major depressive disorder (MDD) mice, whereas normal behaviour resulted from transplantation of healthy colonized from control normal mice. Interestingly the dysregulation in the microbial gene and metabolites of the host occurs primarily in the mice bring depression microbiome which indicated that developing of depression behaviour is occurred via metabolism disruption [7]. From all the above findings, it is obvious that the disruptions in the composition of gut microbiota affects behaviour and vice versa. Findings like that have the offer new approach to developed new treatments for mental disorder condition such as depression and autism.

CONCLUSION

There is a remarkable advance in understanding the role of gut microbiome in regulating neurodevelopment and mental health. This research examining whether gut microbiota and mental disorder are related, via illustration way of interaction between gut microbiota and brain, the role of gut microbiota in regulation of neurological and in the brain development which allowed potential new helpful treatment. This requires applying microbiome analysis on broad human community within life-course studies with more respect to individual differences between people, and further development of analytical approaches is required.

Conflict of interests.

Non conflict of interest

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الخلاصة:

الميكروبيوم هو وفرة هائلة وتنوع من المجتمع الميكروبي الذي يعيش بشكل تكافلي في جسم الإنسان وعلى جسمه. وهي تقدم وظائف مهمة ومفيدة لصحة الإنسان. يعيش معظم الميكروبيوم في الأمعاء ويشارك في تنظيم فسلجة الجسم. وفي الآونة الأخيرة، أصبح الدور المهم للميكروبيوم في تنظيم العديد من الجوانب الفسيولوجية أكثر جاذبية. وعلاوة على ذلك، وجد أن غياب الميكروبات المعوية يسبب حدوث تغيرات مناعية واستقلابية في الحيوانات التجريبية، فضلاً عن تطور عدد من الأمراض المعدية بسبب اضطراب تكوين المجتمع الميكروبي. ومن المثير للاهتمام أن هناك أدلة على أن الميكروبيوم المتعايش يمكن أن يؤثر على نمو الدماغ والإدراك والسلوك من خلال محور الأمعاء والدماغ. علاوة على ذلك، لوحظ أن التغيير في السلوك يمكن أن يؤدي إلى تغيير في تكوين مجتمع الميكروبات المعوية والعكس صحيح، حيث يمكن أن يؤدي التغيير في تكوين ميكروبات الأمعاء المتعايشة إلى سلوك يشبه الاكتئاب. ستناقش هذه المراجعة دور ميكروبيوم الأمعاء في نمو الدماغ. إن فهم آليات التفاعل بين ميكروبات الأمعاء ونمو الدماغ يوفر نهجًا جديدًا لعلاج الأمراض العقلية المختلفة. الاستنتاجات، هناك حاجة لتطبيق تحليل الميكروبيوم على مجتمع بشري واسع النطاق على طول دورة الحياة مع مراعاة الاختلافات الفردية بين الناس، ومزيد من تطوير الأساليب التحليلية.

الكلمات المفتاحية: الأمراض العقلية، نمو الدماغ، ميكروبيوم الأمعاء، محور الأمعاء والدماغ

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