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Gut Instinct: How the Microbiome Affects Traumatic Brain Injury, A Narrative Review

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Abstract

Objectives: Emerging evidence suggests that the gut microbiome may play a role in the pathophysiology of traumatic brain injury (TBI). The objective of this systematic review is to identify and evaluate studies that investigate the relationship between TBI and gut microbiota alterations.

Methods: Using the PRISMA 2020 Checklist, we searched five databases to identify relevant studies. Two independent researchers screened titles and abstracts and identified eligible studies according to the following PICO: studies that investigated the relationship between TBI and gut microbiota AND reported outcomes related to gut microbiome alterations. We assessed the risk of bias for included studies, extracted methodological data and related results of the articles, and used them for qualitative analysis.

Results: We screened the titles and abstracts of 23 identified records and assessed the full text of 10 studies. In total, 5 studies met eligibility criteria and were entered into the qualitative analysis. These studies investigated the effects of TBI on gut microbiota in animal models and human patients. Although, we planned to systematic review, lack of adequate quantitively and qualitative data compelled us to write a narrative survey. The majority of studies reported significant alterations in gut microbiota composition and function following TBI, with potential implications for immune function, inflammation, and neurological recovery.

Conclusion: This systematic review provides evidence supporting a relationship between TBI and alterations in gut microbiota. While the exact mechanisms underlying this relationship remain unclear, these findings suggest that targeting the gut microbiome may represent a novel therapeutic approach for TBI. Further studies are needed to elucidate the mechanisms involved and to evaluate the potential benefits of gut microbiota-targeted interventions in TBI.

Keywords: Gut microbiome, Gut flora, Traumatic Brain Injury, Narrative Review

Abbreviations: TBI: Traumatic Brain Injury; mTBI: mild Traumatic Brain Injury; HPA: Hypothalamic-Pituitary-Adrenal; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; ARRIVE: Animal Research Reporting of *In Vivo* Experiments; GALT: Gut-Associated Lymphoid Tissue; IBS: Irritable Bowel Syndrome; RCTs: Randomized Controlled Trials.

Highlights

- The gut microbiome plays a crucial role in TBI
- Gut-brain communication pathways are disrupted after TBI
- Modulating the microbiome may improve TBI outcomes

Aim of Study

The objective of the review is to investigate the specific aspects of the gut microbiome and its relationship with traumatic brain injury (TBI). The review aims to explore various aspects such as the composition and diversity of the gut microbiome in individuals with TBI compared to healthy individuals, the potential mechanisms by which the gut microbiome influences TBI pathophysiology, and the impact of TBI on the gut microbiome. Additionally, the review aims to examine the potential therapeutic strategies targeting the gut microbiome for TBI management and recovery. By examining these specific aspects, the review seeks to provide a comprehensive understanding of the gut-brain axis in the context of TBI and identify potential avenues for further research and therapeutic interventions. By restoring a healthy balance of bacteria in the gut, it may be possible to mitigate some of the negative effects of TBI. This research could have implications not only for individuals with TBI but for anyone looking to improve their overall health and well-being by optimizing their gut microbiome.

Introduction

Traumatic Brain Injury (TBI) is a condition that affects a significant proportion of individuals worldwide, resulting in substantial medical and financial burdens on healthcare systems. TBI is known to cause ongoing inflammatory processes within the brain and systemic changes to hypothalamic-pituitary-adrenal (HPA) axis function, leading to persistent microglial activation and a range of adverse effects, including cognitive impairments, mental health conditions, and gastrointestinal issues [1].

Notably, adolescents are at the highest risk of sustaining TBI, and research has shown that 20% of young people will experience a mild traumatic brain injury (mTBI) before the age of 16 [2]. Given the importance of this developmental period, adolescents may experience more post-mTBI deficits and require a longer time to recover. However, most research to date has focused on adults, particularly when examining the systemic factors that affect TBI outcomes [3].

According to recent researches, traumatic brain injury (TBI) can affect the gut microbiome and the communication between the brain and gut [4]. This can cause dysbiosis, an imbalance of gut bacteria, and worsen neuroinflammation, leading to changes in the permeability of the intestinal lining and the continuation of deficits caused by TBI [5]. The gut microbiota is essential in maintaining intestinal balance and immune system function by regulating pathways that cause inflammation [6]. Changes to the microbiota can lead to different inflammatory conditions, including issues with behaviour and the nervous system [7-9].

In this context and following narrative review, it is essential to investigate the underlying pathophysiological mechanisms of TBI, particularly in adolescents, to better understand the varied symptoms and inform targeted interventions to mitigate adverse effects. Additionally, exploring the role of the gut microbiome and the brain-gut axis in TBI-induced deficits may provide insights into potential treatment options and preventive measures for individuals who experience TBI.

Methods and Materials

Our narrative review was firstly conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 Checklist.

Information Sources and Search Strategy

We conducted a comprehensive electronic search for studies published until April 9, 2023, in PubMed, Scopus, Web of Science, Embase, and Cochrane library. We developed search strategies tailored for each database, which are detailed in Appendix 1. There were no restrictions on study types, language, or time of publication.

Eligibility Criteria, Selection Process, and Data Extraction

Two independent reviewers screened articles, and any disagreements were resolved by a third reviewer. We included experimental animal studies on traumatic brain injury (TBI) that investigated the gut microbiome using microbiome analysis techniques. We included studies that reported details of the microbiome analysis and evaluated changes in microbiome composition after TBI. We also included studies that investigated the effects of manipulating the gut microbiome on TBI outcomes.

The exclusion criteria were: 1) Review articles, 2) Case reports and case series, 3) Conference abstracts and posters without published paper in peer-reviewed journals. We manually searched the references of the reviewed articles to identify additional related articles.

A pre-defined data extraction form was used, and two independent reviewers extracted data. The form, included information on the study design, TBI model, gut microbiome analysis technique, microbiome composition changes, and TBI outcomes. Disagreements were resolved through discussion or by consulting a TBI and microbiome specialist.

Risk of Bias Assessment

The risk of bias of the included studies was evaluated using the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, which provide a framework for evaluating the quality of animal studies. The guidelines include 20 items that assess the internal validity of animal studies, including animal welfare, experimental design, and data analysis.

Two independent reviewers assessed the studies for risk of bias using the ARRIVE guidelines, and any disagreements were resolved by a third reviewer. Each study was assigned a score based on the number of items that were adequately reported. A total score was computed by adding the number of adequately reported items, and studies that fulfilled at least 50% of the items were considered to be of high quality.

In summary, we aimed to prepare systematic review but after initial analysis reaching this goal is underestimated. Moreover, we decided to write narrative review for effects of TBI on the gut microbiome and the potential for manipulating the microbiome to improve TBI outcomes. We used rigorous methods to identify and assess the quality of studies in this area, and our findings may have important implications for the development of new treatments for TBI.

Discussion

The gut microbiome is a collection of microorganisms that inhabit the gastrointestinal tract and other areas. Referred to recent advances in genomic sequencing, we now have a better understanding of how the gut microbiome develops, what factors affect it, and how it becomes imbalanced in various conditions. Once overlooked as an unimportant part of our bodies, scientists are now fascinated with studying the implications of the gut microbiome on gastrointestinal malignancies as well as its connection to traumatic brain injuries [10]. Though research into this area is still relatively new, there is mounting evidence suggesting that disturbances in gut bacteria play a critical role in TBI-related neuropathology and impaired behavior outcomes. Patients who experience TBI are particularly vulnerable to changes in their gut flora due to antibiotics exposure during treatment or prolonged hospitalization periods coupled with autonomic dysfunction [11].

To assess the influence of gut-associated lymphoid tissue (GALT) on microglial response following TBI, treatment effects such as antibiotics or probiotics can be utilized at 72 hours or 21 days post-injury [12]. Gut dysbiosis resulting from disruption in gut microbiota has been observed to contribute to impaired behavioral outcomes and neuropathology associated with TBI [13] With advancements in genomic sequencing, a better understanding of the determinants and development of gut microbiome under various conditions including TBI is now possible [14] Short-chain fatty acids derived from gut microbiota have demonstrated immune modulating properties along with reducing brain inflammation [15,16].

One alternative explanation postulate that gut microbiota may regulate the blood-brain barrier, leading to potential effects on inflammation and neuronal damage [17] These purported mechanisms are closely linked with inflammatory processes associated with neuropathology following TBI stemming from a compromised gut, indicating possible therapeutic interventions targeting the gut-brain axis as a means of mitigating risk for Chronic Traumatic Encephalopathy and other neurodegenerative disorders [18,19].

By utilizing a bioinformatics methodology, it has been discovered that TBI results in alterations in the quantity of various bacterial groups present within the gut microbiome. The abundance of Agathobacter species was noted to exhibit the most substantial modification [20]. Additionally, there is evidence suggesting that TBI pathophysiology could involve the gut-brain axis and specifically implicate changes in both diversity and composition of the microbiome between individuals who have suffered from TBI versus those who are healthy [21].

In addition, TBI has been shown to disrupt the gut microbiome and alter communication between the gut and brain in animal models resulting in neuronal damage and cognitive impairment [22]. However, numerous studies suggest that targeting the gut microbiome could serve as a means of prevention or treatment for TBI. Probiotic intervention and fecal microbiota transplantation have proven effective at improving cognition in animals with TBIs [23]. This study sought to investigate how depletion of the microbiome prior to repeated mild traumatic brain injury impacts both microbial composition and metabolites within adolescent and adult rats [24]. During the observed time

period, significant changes were identified in both areas, with an increase observed in Erysipelatoclostridium and Clostridium inoculum, while Bacteroides and Clostridium sensu stricto experienced decreases 30 days after exposure to RmTBI. Other alterations were also noted during this time period [24].

Furthermore, the decrease in Bacteroides has been linked to the onset of irritable bowel syndrome (IBS) and has been identified following a stroke [25]. These bacteria play an essential role in upholding the integrity of the intestinal barrier, and their supplementation can lead to increased levels of tight junction proteins [26]. Additionally, reduced quantities of Clostridium sensu stricto have been associated with diminished production of butyrate which is correlated with Alzheimer's disease. As such, removing microbiome prior to RmTBI could potentially trigger pro-inflammatory responses within both gut domains and systemic areas [27]. Moreover, elevated levels of Clostridium inoculum were observed among rats that underwent depleted microbiome during RmTBI treatment; this bacterium is commonly related to antibiotic-induced diarrhoea as well as colitis conditions [24]. Erysipelatoclostridium represents a likely opportunistic species whose increase serves as a biomarker for gastrointestinal infections along with Crohn's disease specifically [28,29].

Research has linked traumatic brain injury (TBI) to schizophrenia, Parkinson's disease, and reduced serotonin production [30,31]. While previous studies have shown a connection between TBI and gastrointestinal issues, recent investigations focus on the gut microbiota's role in post-injury depression and inflammatory, immunological as well as psychological response to brain damage [22]. The study observed that within 24 hours of TBI there was an immediate change in microbial diversity with a significant shift in Lactobacillus family abundance which is known for its psychoactive properties [4,32] Notably identified species such as *L. gasseri, M. formatexigens, E. vetriosum* commonly found in human gut bacteria suggest prospective clinical applications for this research [33].

In their study, Treangen, et al. conducted an investigation into the impact of traumatic brain injury (TBI) on gut microbiome alterations in mice [33]. The researchers utilized QIIME to evaluate changes in bacterial species' relative abundance at baseline and 24 hours post-injury for both TBI and sham groups [33]. Upon comparing the baseline samples of TBI group with those taken 24 hours after injury, significant modifications were observed in four bacterial species' relative abundance. Specifically, *Lactobacillus gasseri, Ruminococcus flavefaciens*, and *Eubacterium ventriosum* exhibited a considerable decrease compared to their baseline levels due to TBI; however, *Eubacterium sulci* and *Marvinbryantia formatexigens* displayed a substantial increase [33]. Additionally, a marked reduction was noted in *Lactobacillus gasseri* among the sham group subjects that indicated possible shared stress response consequences with the experimental group animals subjected to TBI-induced alteration [34].

Multiple investigations have explored how changes within the gut microbiome relate to TBI. Antibiotic treatment after experiencing a brain injury increased cognitive deficits due to disruption in the gut microbiota composition, according to Zhu S, et al. [35] findings from studying mice with TBIs [35]. Taraskina A, et al. [20] work highlighted that fecal transplantation led to enhanced cognition among rats having experienced traumatic brain injuries [20]. Urban RJ, et al. [36] investigation uncovered alterations concerning diversity and composition within patients' gastrointestinal tract post-TBIs when comparing them against healthy controls [36].

According to Romo-Araiza A, et al. [37] the introduction of probiotics may potentially safeguard against cognitive dysfunction resulting from TBI through facilitating growth of advantageous gut microorganisms [37]. Nevertheless, various inadequacies exist within existing literature in this domain. Firstly, most research has been restricted to animal models and cannot be confidently extrapolated to humans. Secondly, there is a need for additional comprehension regarding underlying mechanisms and causal relationships between the gut microbiome and TBI. Lastly, it remains unclear what strategies are best suited for regulating the gut microbiome concerning prevention and treatment of TBI-related issues. As a result, further research that incorporates human subjects and delves deeper into the mechanisms underlying the relationship between further research is needed to address these gaps and provide a better understanding of the potential benefits of prebiotics for alleviating cognitive dysfunction following TBI in humans.

As conflicting result, analyze and highlight any discrepancies or contradictory findings among the included studies. Identify potential reasons for these inconsistencies, such as variations in study design, sample size, experimental models, or methodologies. Discuss the implications of these conflicting results for the overall understanding of the relationship between gut microbiota and traumatic brain injury (TBI).

Identify and discuss the limitations of the studies included in your review. Some common limitations in this field may include small sample sizes, variations in animal models, differences in TBI severity or induction methods, variations in gut microbiota profiling techniques, or lack of standardized outcome measures. Addressing these

limitations helps to provide a balanced perspective and acknowledge the potential biases or shortcomings in the existing research.

Discuss the potential clinical implications of the findings. For example, if the review suggests a consistent association between alterations in gut microbiota and TBI outcomes, discuss the possibility of using gut microbiota as a biomarker for TBI diagnosis, prognosis, or treatment response. Additionally, consider the potential implications for therapeutic interventions targeting the gut microbiota, such as probiotics, prebiotics, or fecal microbiota transplantation, in the management of TBI patients. Highlight any clinical considerations or caveats that need to be addressed before implementing these approaches in clinical practice.

Identify areas that require further investigation or research to address the gaps in the existing literature. For example, discuss the need for well-designed randomized controlled trials (RCTs) to establish causality and determine the efficacy of interventions targeting the gut microbiota in TBI patients. Additionally, identify specific research questions or hypotheses that need to be explored to deepen our understanding of the underlying mechanisms linking the gut microbiota and TBI, such as the role of specific bacterial species, the influence of gut-brain axis communication, or the impact of various interventions on the microbiota-gut-brain axis.

Conclusion

To summarize, the impact of gut microbiome on traumatic brain injury (TBI) is a significant field of investigation with its disturbance potentially causing TBI-related neuropathology and behavioral impairment. Examining how the gut-brain axis functions in relation to TBI could identify promising targets for therapy that lessen risks related to chronic traumatic encephalopathy and other neurodegenerative conditions. Nonetheless, additional research is necessary to elucidate comprehensively the mechanisms behind this relationship while developing optimal techniques for manipulating gut microbiota concerning both prevention and treatment approaches toward TBI.

Ethical Considerations Compliance with Ethical Guidelines

All study methods and consent to participate was approved by ethical committee of Mashhad University of Medical Sciences.

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Competing Interests

The authors have no conflict of interest.

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