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Review

The relationship between the gut-brain axis and migraine

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The gut-brain axis and its role in migraine are increasingly recognized in the scientific community. This mini-review aims to explore the complex interaction between the gut microbiome and the central nervous system (CNS). The gut microbiota communicates bidirectionally with the brain through immune, endocrine, vagal, and other humoral pathways, influencing brain function and contributing to neuroinflammation and immune system disturbances. An imbalance in the gut microbiome can lead to systemic inflammatory responses, disrupted intestinal barrier integrity, and increased intestinal permeability, known as the "leaky gut syndrome." This condition is associated with a pro-inflammatory state that may trigger migraine attacks through the release of cytokines, activation of the trigeminovascular system, and modulation of pain processing pathways in the brain. Key components such as vagus nerve signaling, altered secretion of short-chain fatty acids (SCFAs), and neurotransmitter modulation play critical roles in this axis. The diet also significantly influences the microbiome, with high-fiber diets promoting anti-inflammatory SCFAs, while poor diets contribute to neuroinflammation and increased migraine susceptibility. Emerging evidence suggests that maintaining gut microbiome diversity and stability may alleviate migraine symptoms and enhance quality of life. This review highlights the importance of the gut-brain axis in migraine pathophysiology and suggests that targeting the microbiome could be an adjunctive therapeutic approach for migraine management.

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Introduction

The relationship between the gut and the brain in migraine, while intricate, is increasingly acknowledged within the scientific community. Numerous studies demonstrate a complex interaction between the gut microbiome and the central nervous system (CNS), referred to as the "gut-brain axis" (1–5). The authors intend to conduct a mini narrative review on this subject.

The gut microbiome is defined as the collective array of microorganisms—including bacteria, fungi, viruses, protozoa, and archaea—that reside in the gastrointestinal (GI) tract. The gut microbiota interacts bidirectionally with the brain via several pathways: immune, endocrine, vagal, and other humoral mechanisms. Gut-brain signaling occurs through the production, secretion, and release of hormones, neuropeptides, cytokines, and short-chain fatty acids (SCFAs) (1,5). Concurrently, the CNS can modulate the gut microbiome via sympathetic and parasympathetic pathways, as well as through the release of neuroendocrine peptides (4).

Quantitative and qualitative alterations in the gut microbiome can induce the production of metabolites with cytotoxic effects, promote neuroinflammation, and disrupt immune cell function (1,6). Dysbiosis within the gut microbiota plays a significant role in the pathogenesis of migraine (4). Studies utilizing both animal and human models have shown alterations in the gut microbiome of individuals with migraine when compared to healthy controls (7).

The vagus nerve serves as a crucial communication conduit between the gut and the brain, regulating the impact of microbiome composition changes on cerebral activity and function (7). The vagus nerve is composed of two divisions: afferent (80%) and efferent (20%) pathways. Afferent fibers transmit sensory information from visceral organs, such as the gut, to the brain and are sensitive to mechanical, chemical, and physical stimuli. Vagus nerve stimulation has been shown to prevent and alleviate migraine episodes (5).

The microbiome may also influence the secretion of specific compounds and metabolites by enteroendocrine cells (EECs) through toll-like receptors (TLRs), which signal the innate immune system concerning pain perception. EECs express TLRs that recognize lipopolysaccharides (LPS), and endotoxins produced by bacteria. TLR4 is expressed on afferent vagal fibers and is implicated in LPS detection, potentially activating brain regions involved in pain processing (5).

The intestinal epithelial barrier serves to separate and protect the host from the microbiota through a combination of physical, chemical, immune, and microbial barriers. Various stressors (physical, environmental, or psychological) can lead to dysbiosis (an imbalance in the composition and function of microbial populations), triggering a compromise in the integrity of the intestinal barrier, a condition often referred to as "increased intestinal permeability" or "leaky gut syndrome." This process is accompanied by a systemic pro-inflammatory response, bacterial translocation, disruption of immune homeostasis, and heightened pain sensitivity (4,6).

The gut-brain axis may predispose individuals to migraine attacks in several ways, including alterations in gut microbiome composition, the release of neuropeptides, stress hormones, and inflammatory cytokines (4. Elevated levels of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, arising from "leaky gut," can affect nociceptive responses and activate the trigeminovascular system, thereby increasing susceptibility to migraine onset (3,4).

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis due to stress results in dysbiosis and compromises GI barrier function, leading to changes in intestinal permeability. Activation of the HPA axis initiates cortisol release into the intestinal lumen, subsequently affecting the production of SCFAs and cytokine secretion by immune cells in both the gut and systemically. The release of pro-inflammatory cytokines into circulation is mediated by the gut microbiota and stimulates the release of corticotropin-releasing hormone (CRH), which further induces cortisol release. This cascade of activation and pro-inflammatory cytokine release also alters pain-processing regions in the brain, resulting in central sensitization (5).

The principal trigger for pro-inflammatory immune responses is the translocation of LPS into circulation, stemming from intestinal dysbiosis and increased intestinal permeability. As a result, the inflammatory response may manifest in various regions of the body, including the activation of nociceptors in the trigeminal nerve. It is well established that cytokines mediated by the gut microbiota are elevated during migraine episodes (4).

Circulating LPS and pro-inflammatory cytokines activate CRH production, which increases plasma levels of CGRP (calcitonin gene-related peptide) through the activation of dynorphin and the kappa-opioid receptor in the amygdala. Specifically, CRH stimulates the release of CGRP from trigeminal fibers during a migraine attack, promoting increased glutamate production in the cortex, which may lead to cortical spreading depression (CSD). CGRP further exacerbates alterations in gut microbiome composition and enhances pro-inflammatory mediators, subsequently affecting pain processing pathways in

the brain and contributing to glutamatergic signaling, thereby worsening headache severity (5).

Various bacterial strains are capable of producing glutamate, which can exert a stimulatory effect on nociceptive neurons along the trigeminovascular pathway, playing a critical role in the pathophysiology of migraine and central sensitization. This hypothesis is corroborated by the observation of elevated serum glutamate levels in migraine patients (4).

SCFAs (butyrate, propionate, and acetate) are metabolic products of gut bacteria and are involved in both local and systemic effects, such as glucose homeostasis, satiety, anti-inflammatory actions, and brain signaling. SCFAs, such as butyric acid and propionic acid, travel via the vagus nerve, cross the blood-brain barrier (BBB), and subsequently activate receptors that can alter dopaminergic and serotonergic signaling (1,7). Consequently, it is plausible that the specific production of SCFAs, neurotransmitters, and vagal modulation by the microbiome is intrinsically involved in the regulation of the pain matrix, including hypothalamic pathways (5).

The depletion of bacteria that produce 5-HT (serotonin) and SCFAs in the gut, particularly from the Firmicutes family (including Faecalibacterium prausnitzii, Coprococcus spp., Roseburia spp., Lachnospiraceae spp., Clostridial Clusters IV and XIVa, and Eubacterium hallii), is considered a significant factor in the pathogenesis of migraine (8). SCFAs have been shown to reduce hyperalgesia and diminish the release of TNFα and IL1-β in the intestines of experimental migraine models in rodents (7). Treatment with SCFAs can alleviate intestinal inflammation, resulting in less damage to the intestinal wall and consequently exerting an anti-inflammatory effect in the brain (1,7)

Adults suffering from migraine exhibit a microbiome characterized by lower levels of alpha diversity (a general indicator of gut health) compared to control adults. Fecal samples from over 100 women with migraine have demonstrated reduced populations of butyrate-producing bacteria and, overall, fewer beneficial bacteria (7).

Diet serves as a key regulator of gut microbiota. Depending on dietary composition, the microbiome can vary significantly. Dietary changes can account for more than 50% of the variation in gut microbiota compared to genetic alterations, which explain only about 10% (5).

Fiber-rich diets stimulate the production of SCFAs, which possess anti-inflammatory properties; in contrast, low-fiber diets reduce SCFA production, compromising intestinal barrier function and promoting inflammation and metabolic dysfunction. This dysregulation can activate mechanisms implicated in migraine pathophysiology, including neuroinflammation, serotonergic signaling dysfunction, and neuronal excitability (1,5).

In addition to modulating the microbiota, specific foods influence inflammation, as well as vasodilation and vasoconstriction in the CNS, potentially contributing to pain. The literature has documented a strong association between inadequate dietary habits and migraine. Adequate nutrition is vital for maintaining gut health and ensuring optimal CNS function, thereby playing a critical role in mediating migraine disorders (5).

As elucidated, the gut-brain axis appears to contribute to the triggering of migraines and may serve as an adjunctive treatment. Preserving species richness and microbiome composition, along with enhancing the stability of the microecosystem, may improve pain management and the quality of life for patients suffering from migraine (4).

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