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Deciphering the Pathophysiology of Migraine: Understanding Trigeminovascular System Activity and the Importance of the Gut-Brain Axis

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Abstract

Migraine, a prevalent and disabling neurological condition, manifests in distinct phases: premonitory, aura, headache, postdrome, and interictal. Being a primary contributor to adult disability, it presents a substantial economic challenge on a global scale. Even with extensive research spanning centuries, the complete grasp of its root causes continues to evade us. This intricate neurovascular disorder primarily involves local vasodilation of intracranial and extracerebral blood vessels, coupled with simultaneous stimulation of the trigeminal sensory pain pathway, resulting in headaches. Activation of the 'trigeminovascular system' prompts the release of various vasodilators, notably calcitonin gene-related peptide (CGRP), triggering a pain response. Emerging anti-migraine medications target CGRP signaling by either stimulating 5-HT1F receptors on trigeminovascular nerves (inhibiting CGRP release) or directly blocking CGRP or its receptor. Enhanced delineation of pathophysiological processes holds promise for identifying novel therapeutic targets in migraine prevention. This review thoroughly investigates the physiological processes involved in migraines, highlighting the stimulation of the trigeminovascular system and cortical spreading depression (CSD). Furthermore, it explores the impact of the gut-brain axis on the development of migraines. Inflammation within the trigeminovascular system is believed to contribute to the physiological processes of migraines and might be influenced by inflammation and immune modulation in the gastrointestinal (GI) tract, as suggested by recent studies. Similarly, there is compelling evidence suggesting that the gut microbiota plays a significant role in the bidirectional communication between the brain and the gut, and disruptions in this interaction could be associated with neurological conditions like migraines. A significant source of energy for colonic epithelial cells is the short-chain fatty acids (SCFA); acetate, propionate, and butyrate, which are created in the colon by bacterial fermentation of dietary fiber. Researchers utilized the NTG mouse model to explore the correlation between gut microbiota and migraine. Bridging the knowledge gap between our understanding of migraine pathophysiology and the development of enhanced treatments and strategies for patient management is a critical objective in migraine research.

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INTRODUCTION

Over the last 30 years, there has been a notable increase in the occurrence of migraine, which is among the most widespread neurological conditions globally. According to the Global Burden of Disease (GBD) 2019 Report, the number of people worldwide who suffer from migraines climbed from

721.9 million in 1990 to 1.1 billion in 2019, affecting the physical and mental health of almost 11% of adults worldwide [1, 2]. Migraine is characterized by recurrent headaches that range in severity from moderate to severe, lasting four to seventy-two hours, accompanied by phobias of light, sound, smell, and touch (allodynia, photophobia, phonophobia, and osmophobia) [3, 4].

A person is diagnosed with chronic migraine when they have migraines for three months straight, or at least 15 days out of the month [5]. The activation or perceived activation of the trigeminovascular system is thought to be the cause of the characteristic discomfort associated with chronic migraine. The processing of sensory data from the extracranial and intracranial tissues of the head and face was performed using this system [4].

Migraine can be triggered by a diverse range of factors including specific foods, changes in physical activity, and weather fluctuations. In addition, certain substances or factors can act as migraine triggers under various conditions, making it challenging to establish consistent preventive strategies [6]. This condition has a profound effect on personal health, quality of life, and both economic and social development, with females experiencing a threefold increase in their occurrence [2]. Preliminary indicators such as speech and reading challenges, heightened emotional sensitivity, and sensory hypersensitivity, along with triggers such as fatigue, gastrointestinal issues, stress, sleep disruption, excessive sleep, and hunger, are early manifestations of impending migraines [7, 8]. The prevalence of migraines increases during childhood, particularly during adolescence. In children, the occurrence appears to be unrelated to sex, while in adults, there is a noticeable shift with a female-to-male ratio of 2:1 [9]. Pain, a widespread issue affecting millions of people globally, poses challenges to treatment and has significant implications for mood and social interactions [10]. Altered stress responses create a direct connection with various other medical conditions associated with migraines [11]. Studies at the psychophysical and neurophysiological levels have shown that individuals prone to migraines exhibit heightened vulnerability to sensory stimuli [7]. A sequence of crucial phases, known as the premonitory (prodromal), aura, pain, and postdromal phases, frequently overlap and define migraine symptoms [12]. Migraine episodes unfolded in distinct phases. The prodrome phase, which occurs days prior to a headache, entails significant changes in well-being and behavior. Aura, experienced just before or at the onset of headache and lasting up to 1 h, precedes a moderate-to-intense throbbing headache persisting for 4–72 hours in migraineurs, along with heightened sensitivity to sound and light, as well as nausea and vomiting. The postdrome phase emerges, lasting 24–48 hours, and is marked by fatigue and difficulty concentrating [13].

The established bidirectional communication between the gut and brain, referred to as the microbiome-gut-brain axis, has gained recognition [14]. Recent research has indicated a potential association between headache disorders, particularly migraines, and the gut-brain-immune (GBI) axis, particularly with regard to gastrointestinal (GI) conditions. Given its impact on brain function, the gut microbiome has emerged as a significant factor for understanding the variability and pathophysiology of headache diseases [15]. Recent research has indicated that the gut microbiota may also be important in the regulation of other types of chronic pain, such as inflammatory pain, headache, neuropathic pain, and opioid tolerance, in addition to its critical function in visceral pain modulation [14].

Recent research suggests a connection between headache disorders and the GBI axis in migraine and gastrointestinal (GI) conditions. Given its significance in brain function and immune system control, the gut microbiome may play an important role in elucidating the variability and pathophysiology of headaches [16].

Many conditions can coexist with migraines, including neurological, mental, cardiovascular, gastrointestinal, metabolic endocrine, and immunological disorders. These conditions can activate the trigeminal and neuroendocrine systems. This illustrates that the gut-brain axis, involving the gastrointestinal and neurological systems and intestinal flora, is intricately linked to migraines,

necessitating multi-pathway migraine treatment to identify and eliminate risk factors [17]. Hypothalamic activity modifies brain connections and thalamocortical circuits, which in turn trigger the production of pituitary adenylate cyclase-activating polypeptide (PACAP) and CGRP. Migraine symptoms are eventually caused by intracerebral vasodilation, which is triggered by PACAP release. It is now commonly acknowledged that CGRP contributes to the two-way interaction of the gut-brain axis. Dysbiosis can increase CGRP release and has an antibiotic impact on gut bacterial strains, such as *Escherichia coli*, *Lactobacillus acidophilus*, and *Enterococcus faecalis* [18].

This review explores the diverse mechanisms that trigger migraine, with a particular focus on the activation of the trigeminovascular system. We explored the effect of various neuropeptides, including CGRP and PACAP, on migraine episodes. Additionally, this study examined the role of the gut microbiota in the development of migraine.

PATHOPHYSIOLOGY OF MIGRAINE

The physiological processes of migraine remain intricate and have not been fully elucidated, encompassing the intricate anatomy and physiology of the neural structures responsible for pain genesis and regulatory pathways. A comprehensive analysis is essential to understand the underlying mechanisms. Numerous studies have proposed diverse hypotheses, sparking considerable debate between neural- and vascular-based migraine models. Nevertheless, the precise mechanisms underlying migraines remain unclear. A widely acknowledged mechanism in migraine involves the activation of the trigeminovascular system, playing a pivotal role in the onset of headaches [19]. The diagram given below depicts various migraine-triggering mechanisms (Figure 1). Here, we emphasize mechanisms such as the activation of the trigeminovascular system and cortical spreading depression.

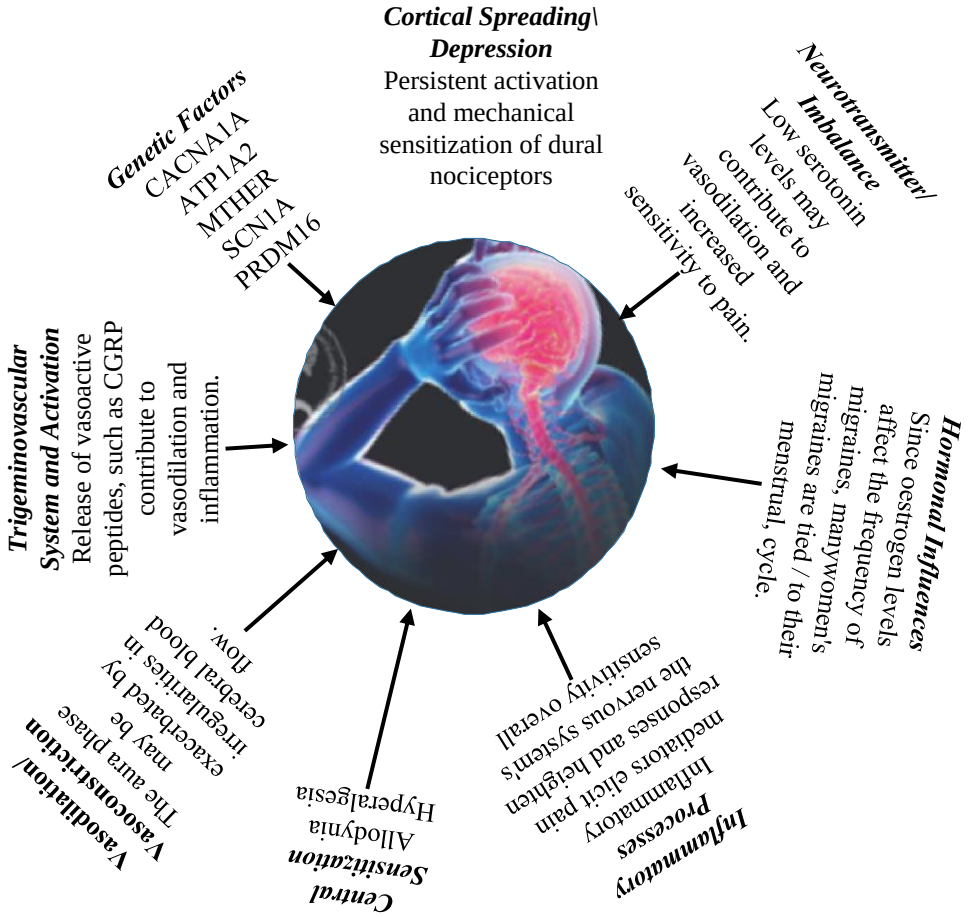

Figure 1. Various migraine-triggering mechanisms.

ACTIVATION OF TRIGEMINOVASCULAR SYSTEM

Regardless of the original cause of migraine, the trigeminovascular system is thought to be activated by headaches. The pial and dural meningeal veins are innervated by the primary sensory fibers of the trigeminal nerve, which forms the core of this system. Peripheral mechanisms, such as the release of inflammatory mediators and agents during neurogenic inflammation, cortical spreading depression (CSD), or a combination of both, are likely involved in the activation of the trigeminovascular system [8]. The cranial dura mater is deeply innervated by afferent nerve fibers, which may contribute to the development of headaches. As observed in migraine headaches, the activation of these nerve fibers can cause referred pain and discomfort outside the head [9]. The peripheral trigger for migraine pain is the stimulation of nociceptive neurons innervating the dura mater, which results in the release of vasoactive peptides such as PACAP-38, CGRP, substance P, and vasoactive intestinal peptide (VIP) [20]. The initial proposition that neurogenic inflammation in the peripheral nervous system serves as a source of migraine pain was reconsidered. This reassessment primarily stems from the observation that medications that inhibit plasma protein extravasation, a characteristic of inflammation, have proven ineffective in treating migraine during clinical trials. Although there is ongoing discourse regarding trigeminal activation and linked neurogenic inflammation in the context of migraines, there is currently no direct evidence supporting the existence of an inflammatory component within the dura mater in migraine cases. The meninges and cerebral blood vessels are innervated by peripheral axons originating from the trigeminal ganglion, which constitute the trigeminovascular system. The trigeminocervical complex (TCC) is formed by the combination of the spinal trigeminal nucleus caudalis and the upper cervical spinal cord, where axons converge centrally [21]. Previous studies have indicated that stimulating the trigeminovascular network is a significant trigger for migraines. The activation of trigeminal neurons in animal models leads to the release of neuropeptides, promoting plasma extravasation, platelet activation, mast cell degranulation, and meningeal dilation. All these are hallmarks of neurogenic inflammation [22]. Vasoactive peptides, including CGRP, substance P, VIP, and PACAP-38, are released when nociceptive neurons innervating the dura mater are aroused, which is the first step in peripheral stimulation of migraine pain [23]. Reports have indicated increased levels of CGRP in jugular venous plasma during migraine attacks, whereas substance P does not exhibit a similar elevation. This increase in CGRP levels is likely indicative of significant stimulation leading to the release of CGRP from the trigeminal afferents [24]. In this context, the focus is on CGRP, PACAP, and vasoactive peptides, excluding substance P. Here, we present the factors influencing factors migraine and trigeminal activation in migraine (Figure 2).

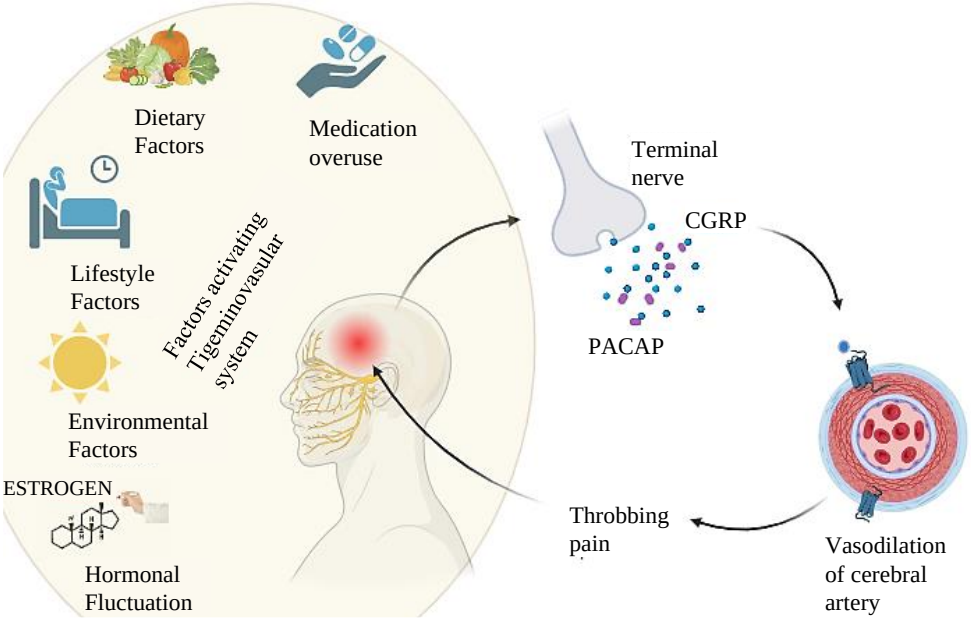

Figure 2. Modifiable factors affecting migraine and trigeminal activation of migraine.

EFFECT OF VASOACTIVE PEPTIDE IN MIGRAINE PATHOLOGY

CGRP

Nociceptors, which are found in external organs, such as the skin, muscles, joints, bones, and deep visceral tissues, are responsible for initiating pain. The dorsal root ganglia (DRG) and trigeminal ganglia (TG) contain nociceptors, which are the peripheral nerve ends of specific sensory neurons. The dorsal horn of the spinal cord receives nociceptive signals from these nociceptors, which translate unpleasant stimuli (such as inflammation, high temperatures, or mechanical injuries) into nerve impulses [14]. The large cerebral arteries and meninges are innervated by nociceptive fibers. The primary pathway for nociceptive innervation is the ocular branch of the trigeminal nerve [20].

The primary features of neurogenic inflammation in migraine include the release of neuropeptides from the trigeminal nerve, such as substance P and CGRP, which cause mast cell degranulation, extravasation of plasma proteins, and dilatation of the arteries. This cascade of responses may also involve pro-inflammatory cytokines and chemokines [25]. However, migraine prevention has several limitations. Drugs such as beta-blockers, calcium channel blockers, antiepileptics, and antidepressants, which were not specifically designed to treat migraines, were used earlier in 2018 and saw the introduction of monoclonal antibodies targeting CGRP, the first migraine-specific preventives [26].

Patients with migraine have serum levels of pro-inflammatory cytokines, such as interleukin-1β and tumor necrosis factor-alpha. These cytokines may affect trigeminal nerve nociceptors, which may precipitate migraine attacks. Statistically significant associations have been observed between migraine and a range of inflammatory problems, including allergies, asthma, obesity, metabolic syndrome, and gastrointestinal disorders.

CGRP is a neuropeptide that is extensively expressed in the peripheral and central trigeminovascular systems and is implicated in the modulation of craniofacial nociception [27]. Strong dilatator characteristics and widespread expression in both the distal and cerebral neurons characterize CGRP. Additionally, it has a regulatory action on second and third-order neurons, which seems to be the foundation for its modulatory activity in the mechanisms underlying central pain [21]. A 37-amino acid peptide known as CGRP can bind to the CGRP receptor, which is made up of three subunits: the receptor component protein (RCP), the calcitonin receptor-like receptor (CLR), and receptor activity modifying protein 1 (RAMP1) [28]. The central nervous system (CNS) and somatosensory peripheral nerves have significant levels of expression for the α-isoform of the neuropeptide CGRP, while motor neurons and the enteric nervous system are the primary sites of expression for the β-CGRP isoform. An increasing amount of research suggests that CGRP in the trigeminovascular system is a key mediator of migraine [29]. CGRP acts centrally in the trigeminal ganglion and may play a role in inter-ganglion signaling. In addition to causing arterial vasodilatation, the peripheral release of CGRP in the meninges can activate meningeal nociceptors and promote sterile inflammation [23].

CGRP is stored in vesicles within the sensory nerve endings of the CNS. When trigeminal axons release CGRP into meningeal blood vessels, it leads to their dilation and triggers the activation of trigeminal neurons. Moreover, CGRP acts on glial cells, dural mast cells, and various neurons in both the CNS and peripheral nervous system. This initiates a cascade of events, including neuroinflammation, allodynia, and other sensory effects specific to migraines [30]. According to data from clinical trials, the 5-hydroxytryptamine1B/1D agonist sumatriptan and other triptan medications successfully cure migraine headache discomfort by bringing CGRP levels back to normal [31] For the prevention and treatment of episodic and chronic migraines, three types of medicines that target the CGRP system have received approval. Initially, there were monoclonal antibodies specifically aimed at CGRP, monoclonal antibodies targeting the conventional CGRP receptor, and small-molecule antagonists of CGRP receptors known as antagonists [30].

PACAP

PACAP is a biologically active neuropeptide that belongs to the VIP/secretin/glucagon family., PACAP27 and (mostly) PACAP38, are biologically active. It is a pleiotropic peptide that functions in the neural system as a neurotransmitter, neuromodulator, and hormone in the pituitary gland] [32]. Over the past ten years, a growing body of research has indicated that PACAP38 plays a crucial role in the pathophysiology of migraine. Similar to CGRP, PACAP38 is found near sensory nerve fibers, dilates cranial arteries, and, when administered to patients, induces migraines [33]. PACAP (in its two variants) binds to three distinct receptors: VPAC1, VPAC2, and PAC1, which interact with PACAP [34]. The most plausible reason for the development of migraine following PACAP-38 administration appears to be the modulation of extracranial or dural trigeminal nociceptors, which are not part of the blood-brain barrier. Thus, a critical step in the chain of events leading to the development of migraines may be the increase in intracellular cAMP levels in dural nociceptors that occur after PAC1 activation [35]. Although they perform comparable tasks, PACAP and CGRP most likely play different roles in the development of migraine-like symptoms. Since these pathways appear to function independently in rodent models, elevated levels of these chemicals in the peripheral blood during migraine attacks could potentially be used as biomarkers [36].

VIP

Vasoactive peptides activate smooth muscle cell receptors, which leads to potassium channel opening and vasodilation. VIP and PACAPs induce cranial artery dilation primarily via VPAC1 and VPAC2 receptors. A 2-hour VIP infusion and prolonged stimulation may increase potassium channel openness and ion efflux, leading to depolarization and activation of the trigeminal pain pathway, potentially explaining migraines [37]. The vasoactive intestinal polypeptide /glucagon/secretin family also comprises related peptides like PACAP, GIP, glucagon, and secretin. VIP's biological actions of VIP are mediated by VPAC1 and VPAC2 receptors, with PAC1 receptors playing a significantly smaller role [38]. Within 20 min of infusion. Experimental trials in migraineurs without aura have demonstrated that PACAP isoforms trigger migraine episodes. In contrast, VIP does not result in migraines or structural alterations to the arterial wall; instead, it temporarily dilates the superficial temporal and middle meningeal arteries. VIP's weak vasodilatory response may account for its poor ability to induce migraines [37]. VIP's potential significance in migraine pathogenesis is still up for discussion.

CORTICAL SPREADING DEPRESSION

For the first time, Aristides Leão (1944) described CSD, as a wave of depolarization that moves slowly over the neuronal and glial membranes. After the gradual depolarization wave, there was subsequent suppression of cortical activity was suppressed for up to 30 min. This depression is accompanied by a hyperemic wave, followed by an extended period of reduced blood flow in the cortex. [19]. Various clinical and neuroimaging observations substantiate the idea that CSD serves as the pathophysiological counterpart to the neurological symptoms observed in migraine aura [39], and induces local microenvironment changes, including disruption of adenosine triphosphate, glutamate, potassium, nitric oxide, and CGRP dynamics. Repetitive depolarization and repolarization of hyperexcitable neurons lead to extracellular potassium (K+) buildup, causing disturbances in cell membrane ionic gradients, sodium (Na+) and calcium (Ca2+) influx, and glutamate release. However, the exact mechanism of CSD propagation remains unclear. Initially, K+ accumulation or abnormal glutamate diffusion was thought to drive it. Later, the authors suggested the involvement of gap junctions between the neurons and glial cells. This depolarization wave alters cerebral blood flow, causing vasodilation and hyperemia. Despite ongoing debates regarding the impact of CSD on the trigeminovascular system, studies on the visual cortex of mice have indicated that focal stimulation triggers CSD, releasing pro-inflammatory molecules via neuronal pannexin 1 megachannels. This process activates meningeal nociceptors and suppressing this pannexin-1-dependent cascade eliminates CSD-induced trigeminovascular activation, dural mast cell degranulation, and headaches [19].

Migraine and the Gut-Brain Axis

There are many different types of bacteria in the gastrointestinal tract (GIT) that constitute the gut microbiota. Recently, owing to the bidirectional connectivity of the bacterial community to the brain and other parts of the body, the importance of gut microbiota to human health has been recognized [40]. The phrase "gut-brain axis" refers to the reciprocal interaction between the CNS and the gastrointestinal system (GI), neurological conditions such as multiple sclerosis, anxiety and mood disorders, Parkinson's disease, Alzheimer's disease, and migraines, are brought on by any malfunction to this system. Additionally, several neurotransmitters such as gamma-aminobutyric acid, dopamine, serotonin, and CGRP have been proposed as potential players in this process. Psychological and physical stressors can alter the composition of the gut microbiota. These stressors trigger the release of corticotrophin-releasing hormones in the hypothalamus, leading to the secretion of cortisol from the adrenal glands. This hormonal reaction may prompt changes in intestinal permeability by affecting the profile of the microbiota [15]. The gut microbiota, comprising approximately 10^14 organisms, exhibits a gene count approximately 100 times that of the human genome. Gut bacteria play a crucial role in secreting neurotransmitters; synthesizing metabolites and endotoxins; and regulating the permeability, structure, and function of the mucosa, thereby contributing to the normalization of GI tract function [41].

The host receives nutrition from microbes, and it is becoming increasingly evident that the microbiome influences host behavior and health by producing serotonin, which travels from the gut to various parts of the body. A major component of the gut-brain connection is the bidirectional vagus nerve, which has recently been demonstrated to physically contact enteroendocrine cells in the gut epithelium to directly govern the function from the gut to the brain [42]. Communication between the gut microbiota and brain occurs through the vagus nerve, which comprises two divisions: afferent and efferent pathways. Afferent fibers transmit sensory information from the visceral organs, such as the gut, to the brain. These afferent vagal fibers respond to mechanical, chemical, and physical signals. Stimulation of the vagus nerve has been identified as a means to prevent and alleviate migraine episodes [43]. The CNS can impact conditions within the intestines via the gut-brain axis, regulating factors such as intestinal movement, waste elimination, and mucosal immune responses. Communication between the brain and gut microbiota primarily occurs through the vagus nerve, tryptophan metabolites, and microbial byproducts such as short-chain fatty acids (SCFAs) or peptidoglycan [44].

Afferent sensory nerves engage polysynaptic inputs to higher brain areas, such as the limbic forebrain and hypothalamus, facilitating visceral signals from the intestines to the spinal cord and the solitary tract. The cingulate and insular cortex, amygdala, and hypothalamus alter autonomic efflux to the viscera, enabling bidirectional control of the gut-brain axis [45].

Enteroendocrine cells (EECs) indirectly regulate GI motility, intestinal permeability, secretion, and food intake by communicating with vagal afferent fibers. Specifically, enterochromaffin cells within the gut, a type of EEC, secrete neurotransmitters, such as serotonin (5-HT). Vagal afferent fibers interact with EEC-secreted compounds, including 5-HT, and gut hormones such as somatostatin and cholecystokinin. This release activates brain pathways, such as the nucleus tractus solitarii in the medulla. Additionally, the microbiota can influence EEC secretion via toll-like receptors (TLRs), crucial for innate immune system signaling and pain perception [43]. Changes in gut microbiota may have an impact on migraine pathogenesis, according to new research. When 42 individuals with EM were compared to 43 healthy controls in a cross-sectional, case-control study, the gut microbiota of the EM participants was altered. Additionally, patients with fibromyalgia and irritable bowel syndrome (IBS) have altered gut microbiota, which may indicate a connection between the gut microbiota, pain, and pro-inflammatory mediators. The idea that microbiota dysbiosis increases migraine-like pain is supported by a recent preclinical investigation that showed increased levels of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNFα) in the intraspinal trigeminal nucleus caudalis (Sp5C) [46].

Impact of Gut Microbiome and its Metabolites on Migraine Pathophysiology

An increasing number of studies have shown that changes in the balance of the intestinal microbiota influence immune system development and gastrointestinal processes as well as migraine. Various forms of pain, such as spinal cord, visceral, IBS-associated discomfort, migraine, and occasional headaches, appear to be influenced by the microbiota composition [47]. A growing body of research indicates that the gut microbiota releases substances that affect specific neural pathways within the gut-brain axis, alongside molecules that bind to pattern recognition receptors. Also, numerous neurotransmitters and neuromodulators can be produced by them [48]. A meta-analysis has demonstrated the correlation between *Helicobacter pylori* infection and migraine, with *H. pylori* infection present in 45% of migraineurs and 33% of healthy control subjects. Inflammatory and vasoactive substances are thought to be produced by *H. pylori* infection, which is associated with a chronic, ongoing inflammatory state. Significant alterations in the quantitative makeup of certain resident microorganisms were discovered by Kopchak et al. in another investigation comparing migraineurs with healthy individuals. Patients with migraine had higher concentrations of *Alcaligenes spp*., *Clostridium propionicum*, *Clostridium coccoides*, *Eggerthella lenta, Pseudonocardia spp.*, and *Rhodococcus spp*. than those in the healthy group. Patients with migraine had higher levels of fungi like *Candida* and *Micromycetes* species than those in the control group did [47]. A total of 108 shotgun-sequenced fecal samples from elderly patients with migraine and matched healthy controls were examined in a metagenome-wide association study. In the migraine group, the alpha diversity was significantly lower at the species, genus, and orthologous levels (Kyoto Encyclopedia of Genes and Genomes). *Firmicutes*, particularly *Clostridium spp*., were markedly enriched in the migraine group. In contrast, healthy controls had higher concentrations of advantageous bacteria including *Bifidobacterium adolescentis*, *Methanobrevibacter smithii*, and *Faecalibacterium prausnitzii* [48].

Bacterial pathogens, particularly *Streptococcus pyogenes* and *Staphylococcus aureus*, can directly stimulate pain receptors known as nociceptors. In skin and soft tissue infections, *S. pyogenes* releases a toxin called streptolysin S (SLS), which activates specific nociceptors (TRPV1). This activation results in a pain sensation. Similarly, *S. aureus* in subcutaneous infections produces pore-forming toxins such as alpha-hemolysin (Hla), HlgAB, and PSMa. These toxins lead to the generation of action potentials that affect pain perception. This process can also induce mechanical allodynia, which is a heightened sensitivity to pain from normally nonpainful stimuli [49].

Colonic epithelial cells rely heavily on SCFA such as acetate, propionate, and butyrate, which are generated through bacterial fermentation of dietary fiber in the colon. Researchers employed the NTG mouse model to investigate the link between gut microbiota and migraine. They investigated the effect of SCFAs administration on NTG-induced migraine-like pain and gut function. These findings indicated that SCFA treatment reduced NTG-induced hyperalgesia in both the tail-flick and formalin challenge tests. Additionally, SCFA treatment led to a decrease in the release of the pro-inflammatory cytokines TNFα and IL1-β in the intestine following NTG injection. Notably, SCFA treatment demonstrated the ability to alleviate inflammation in the gut, consequently reducing intestinal wall damage and preventing NTG-induced loss of neurons in the trigeminal nucleus. The study outcomes suggest that SCFAs could serve as a promising therapeutic approach for migraine and related intestinal disorders [50], as butyric acid and propionic acid travel through the vagus nerve, cross the blood-brain barrier (BBB), and activate receptors that potentially influence dopaminergic and serotonergic signaling. This suggests that gut microbes intricately regulate the pain matrix, including the hypothalamic pathways, through specific SCFA production, neurotransmitters, and vagus nerve modulation [43].

A study related to butyrate and CGRP showed that higher doses of butyrate (1 mmol/L, 10 mmol/L) when exposed to primary cultured rat DRG neurons over an extended period (48 h) sensitized the release of excitatory neuropeptides SP and CGRP, created by capsaicin [51] VIP and neuropeptide Y (NPY), and are believed to have antimicrobial effects on various gut bacterial strains, including *Escherichia*

coli, *Enterococcus faecalis*, and *Lactobacillus acidophilus*. This suggests their potential involvement in the bidirectional relationship between the gut and the brain [52].

Leakage of lipopolysaccharides (LPS), bacterial metabolites from the intestinal lumen into the bloodstream, serves as a potent trigger for pro-inflammatory immune responses. Increased levels of LPS entering circulation occur when there is heightened intestinal permeability, often referred to as a "leaky gut." Depending on the genetic predisposition, these pro-inflammatory responses may manifest in different areas of the body, potentially impacting nociceptors of the trigeminal nerve in the case of migraines [53]. Key migraine-related pathways, such as serotonergic transmission, CGRP activity, and cortical activation, are indirectly connected to the gut flora [53].

To confirm the involvement of the gut-brain axis in migraines, an alternative approach involves examining nitric oxide (NO) production, which is directly released into the brain through trigeminal neuron excitation. There is a possibility of an indirect effect on the enteric system, as NO crosses the BBB and reaches the intestine. Notably, NO synthesis increases during NTG-induced migration, primarily in its neuronal form (nNOS), released under CNS control, and spreads through the peripheral nervous system, including the enteric nervous system (ENS). Conversely, SCFAs decrease NO synthesis and release in intestinal tissue layers without activating the neuroinflammatory cascade [54].

CONCLUSION

Migraine is a hereditary neurological condition marked by an inherently increased sensitivity of the cortical and subcortical networks, intensifying the perception of sensory stimuli. Migraine episodes typically follow a sequence of premonitory, headache pain, and postdromal phases, with approximately one-third of individuals experiencing reversible sensory, visual, and language symptoms during the aura phase. Existing evidence emphasizes the role of the gut-brain axis in migraine, although the specific mechanism remains unclear. This dynamic is shaped by multiple factors, including the composition of the neuropeptide intestinal microbiota, inflammatory mediators (IL-1β, IL-6, IL-8, and TNF-α), stress hormones, nutritional substances, and the serotonin pathways.

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