Gut microbiota and migraine

Joshua Crawford, Sufang Liu, Feng Tao [*]

Department of Biomedical Sciences, Texas A&M University College of Dentistry, Dallas, TX 75246, USA

ABSTRACT

Migraine is a leading cause of disability among the adult population and is a significant burden on the economies of the world. Studies into the underlying causes of migraine have spanned centuries but its underlying mechanisms are still not fully understood. In recent years, accumulating evidence implicates that microbiota-mediated gut-brain crosstalk may contribute to the pathogenesis of migraine. This review provides a brief account of the history of migraine theories and summarizes the recent studies showing how gut microbiota is involved in the pathophysiology of migraine. Future research perspectives for better understanding the role of the gut microbiota in migraine are also discussed.

Introduction

Migraine is a common and debilitating neurological disorder. Results from recent national health surveys in the United States indicate that more than 15% of the adult population suffer from migraine with 21% of women and 10.7% of men affected (Burch et al. 2018; 2021). Annual direct economic costs of migraine morbidity have been calculated to exceed 9 billion dollars per year (Raval and Shah 2017). The International Headache Society has classified migraines into two primary categories: with and without aura. Diagnostic symptoms of migraine include at least 5 attacks lasting 4–72 h, unilateral location, pulsating, pain, worsening by physical activity, nausea/vomiting, and photophobia (Burch et al. 2018). Additionally, 15–20% of migraine sufferers report experiencing sensory disturbances, such as visual changes or feelings of numbness preceding the migraine, which is referred to as aura (He et al. 2015). The mechanisms underlying migraine are still unclear and have been debated since the 1800 s. The first mechanism was postulated by a physiologist, Emil Heinrich Du Bois-Raymond, who proposed that migraine is a disorder of the spinal cord in which the ciliospinal center (C8-T2) sympathetic nerves are activated to cause a vasoconstriction that leads to pain and migraine symptoms on the opposing side of the body (Koehler and Isler 2002). Almost immediately this theory was countered by another physiologist, Charles-Edouard Brown-Sequard (Koehler 1995). From his own experiments on the spinal cord, Brown-Sequard did not believe sympathetic activation could be the cause of migraine, and instead he thought that migraine is caused by a paralysis of the sympathetic system that results in vasodilation (Koehler 1995). English physician P.W. Latham then combined these

theories and proposed that migraine is caused first by a vasoconstriction followed by vasodilation (Latham 1873). This vascular theory of migraine became cemented in the migraine literature when clinical evidence of vasodilation in patients with migraine was reported by Mollendorff in 1867 (Möllendorff 1867). Then in 1868 Edward Noakes reported the use of a vasoconstricting agent, ergotamine, which could successfully treat the symptoms of what he called neuralgia (Woakes 1868). However, a litany of scientific evidence in the last 30 years has come out to call into question the validity of a vascular origin of migraine. In 1990, Olesen et al. showed that blood flow changes were unrelated to the pain phase in migraine (Olesen et al. 1990). In 2007, Rahmann and colleagues reported that infusion of vasoactive intestinal peptide caused a significant vasodilation but not migraine in migraineurs (Rahmann et al. 2008). If not a vascular disorder, what could be the underlying mechanisms causing migraine?

What is not debated is the importance of the trigeminal system in the pathophysiology of migraine. Moskowitz and co-workers first hypothesized in 1979 that the trigeminal nerve was involved in migraine through release of a vasoactive peptide, Substance P (Moskowitz et al. 1979). While the studies listed previously cast doubt on the importance of the vascular nature of trigeminal nerve activation or vasoactive peptides, numerous studies have shown that trigeminal nerve activation and vasoactive peptides are nonetheless involved in migraine pathology, implicating the peripheral and central neural pathways as the culprits (Ashina et al. 2019; Cernuda-Morollón et al. 2013; Sarchielli et al. 2000). In recent years, a breakthrough in migraine pathophysiology and treatment came with the discovery of the importance of calcitonin gene-related peptide (CGRP) in migraine. Over half of neurons in the

trigeminal ganglion contain CGRP and tracing studies have shown that fibers containing CGRP originate in the trigeminal ganglion and co-localize with Substance P (Edvinsson et al. 1989; Eftekhari et al. 2010). CGRP release by afferent neurons in the periphery and in the outer laminae of the trigeminal nucleus caudalis is mediated by the activation of transient receptor potential vanilloid 1 (TRPV1) (Goadsby and Edvinsson 1993; Meng et al. 2009). CGRP release also modulates immune function (Holzmann 2013). In migraine patients, CGRP has been shown to be released during migraine attacks and medications for migraine treatment, such as triptans, have been shown to inhibit CGRP release (Goadsby et al. 1990). Following these discoveries, monoclonal antibody against CGRP and CGRP receptor antagonist have been developed and approved by the United States Food and Drug Administration for the prevention and treatment of migraine (Rivera-Mancilla et al. 2020).

Interestingly, an association between migraine and gastrointestinal (GI) disorders has been observed (Cámara-Lemarroy et al. 2016). As mentioned above, nausea and vomiting are common symptoms in patients with migraine. A higher prevalence of headache was found in individuals with high reflux, diarrhea, constipation, and nausea (Aamodt et al. 2008), and this study also found that gastrointestinal complaints increased with increasing headache frequency. Additionally, more and more studies have shown a higher incidence of migraine in patients with irritable bowel syndrome (IBS) (Chang and Lu 2013). A population study in 1992 reported that in 350 IBS sufferers, 32% complained of migraine headaches compared with 18% of controls (Jones and Lydeard 1992). A later prospective study found similar results with 17% of IBS patients reporting having migraines compared with only 8% in controls (Vandvik et al. 2004). Gastroparesis, delayed stomach emptying, is another GI disorder that has long been linked to migraine. Boyle, Behan, and Sutton observed that gastric emptying time was significantly correlated with intensity of headache, nausea, and photophobia in patients undergoing a migraine attack (Boyle et al. 1990). Of note, a significant number of migraine sufferers report a specific food as a migraine trigger. A survey by Peatfield et al. in 1984 revealed that among their migraine patients, 19% reported chocolate as a trigger, 18% identified cheese as a trigger, and 11% observed that citrus fruit can cause migraine attack (Peatfield et al. 1984). With diet being a major environmental factor affecting the composition of gut microbiota, a link between food and migraine may suggest the involvement of gut microbiota in migraine (Moschen et al. 2012).

With migraine being firmly recognized as a neurological disorder, the notion that the gut microbiota could be involved with migraine should not be surprising as we have learned about its contribution to other neurological disorders. For instance, Alzheimer's disease is a neurodegenerative disorder characterized by production and deposition of amyloid-β-peptide (Aβ) in brain tissues from the cleave of amyloid precursor protein (APP) (Murphy and LeVine 2010). In an APP transgenic mouse model, the Alzheimer's transgenic mice showed significantly different gut microbiota compared with wild-type control mice (Bäuerl et al. 2018). Patients with Alzheimer's disease have altered gut microbiota, specifically, lower amounts of butyrate-producing bacteria as well as more pro-inflammatory bacteria (Zhuang et al. 2018). Another neurodegenerative disease with evidence linking the gut microbiota to its pathogenesis is Parkinson's disease (Keshavarzian et al. 2020). In Parkinson's disease, dopaminergic neurons in the basal ganglia and substantia nigra are depleted which leads to motor-related symptoms, such as tremor, stiffness, and postural instability (Alexander 2004). A recent *meta*-analysis of gut microbiota from Parkinson's patients revealed significant reductions in bacteria that produce short-chain fatty acids and an overall microbial composition that is linked to a pro-inflammatory state (Romano et al. 2021).

The exact mechanisms underlying how gut microbiota is involved with neurological disorders, in general, and in migraine specifically, are unknown. The nature of gut microbiota studies in humans is more correlative than causative. In the human studies, fecal samples were collected from participants for sequencing. Numerous different types of sequencing are used depending on the goals of the studies. The most common sequencing methods are 16 s rRNA sequencing and metagenomic sequencing. From the sequencing results, researchers can evaluate the abundance and diversity of the microbiota (Qian et al. 2020). In gut microbiota studies using animal models, researchers have provided insight into the underlying mechanisms in addition to information about abundance and diversity, and it is possible to investigate the roles of specific groups of bacteria or gut microbiota composition in relation to disease through the use of germ-free mice and targeted manipulation of the gut microbiota (Kennedy et al. 2018).

It is important to note that besides gut microbiota, other relevant mechanisms for migraine could include gut-derived molecules leaking through the intestinal wall and traveling to the central nervous system through the circulatory system or gut-derived hormones modulating the hypothalamic, pituitary, adrenal axis (Arzani et al. 2020). Inflammatory cytokines, including interleukin 1β and interleukin 6, have been shown to be released by regulatory B cells in response to perturbation of the microbiome (Rosser et al. 2014). Zanos and colleagues further found that vagal nerve activity could be directly modulated by intraperitoneal injection of inflammatory cytokines (Zanos et al. 2018). It has also been shown that vagal nerve fibers innervating the gut express free fatty acid receptor 3 (FFAR3) (Cook et al. 2021). FFAR3 is known to be involved with gut microbiome-derived short-chain fatty acid signaling.

In this review, we summarize direct and indirect evidence from recent studies that reveal a potential role of gut microbiota in the pathogenesis of migraine (Fig. 1).

Literature searching criteria

We performed a title and abstract search in PubMed using the following keywords: *microbiome* and *migraine*, *microbiota* and *migraine*, *diet* and *migraine*, and *vagus nerve* and *migraine*. Searches were limited to papers that were published in English or where there was an English translation available.

Direct evidence of gut microbiota involved in migraine

Several lines of evidence have demonstrated that gut microbiota plays an important role in the development and maintenance of migraine.

Nitroglycerin (NTG) treatment in rodents has been used to model migraine after it was found clinically that a large percentage of patients being treated with nitrile drugs experience headache. The NTG model shares important features with what is seen in human migraine patients such as shared pain behaviors, central sensitization, and cortical spreading depression (de Tommaso et al. 2004; Knapp et al. 2017; Long et al. 2020). Rodent models employing single and chronic administration of NTG show both facial and hindpaw hypersensitivities as well as photophobia (Anapindi et al. 2019; Bates et al. 2010; Casili et al. 2020; Farajdokht et al. 2017; Farkas et al. 2016; Guo et al. 2021; Moye et al. 2019; Pan et al. 2022; Shu et al. 2020; Tang et al. 2018; Zhang et al. 2020a). However, there are also aspects of the model that raise concern. For instance, mice need a supraphysiologic dosage of NTG to induce migraine-like pain behaviors and do not show spontaneous pain. Further, animal studies have reported mechanically-induced hyperalgesia with NTG treatment while human studies report mechanically-induced allodynia (Burstein et al. 2000; Cuadrado et al. 2008). While these are both symptoms of central sensitization, mechanically-induced allodynia needs to be confirmed in animal NTG model of migraine.

In our recent study, we investigated such role of gut microbiota using a NTG-induced migraine mouse model (Tang et al. 2020). We observed that 10-day broad-spectrum antibiotic treatment via oral garage prolonged facial mechanical hypersensitivity produced by intraperitoneal injection of NTG and enhanced NTG-increased the expression of tumor necrosis factor-alpha (TNFα) in the spinal trigeminal nucleus caudalis
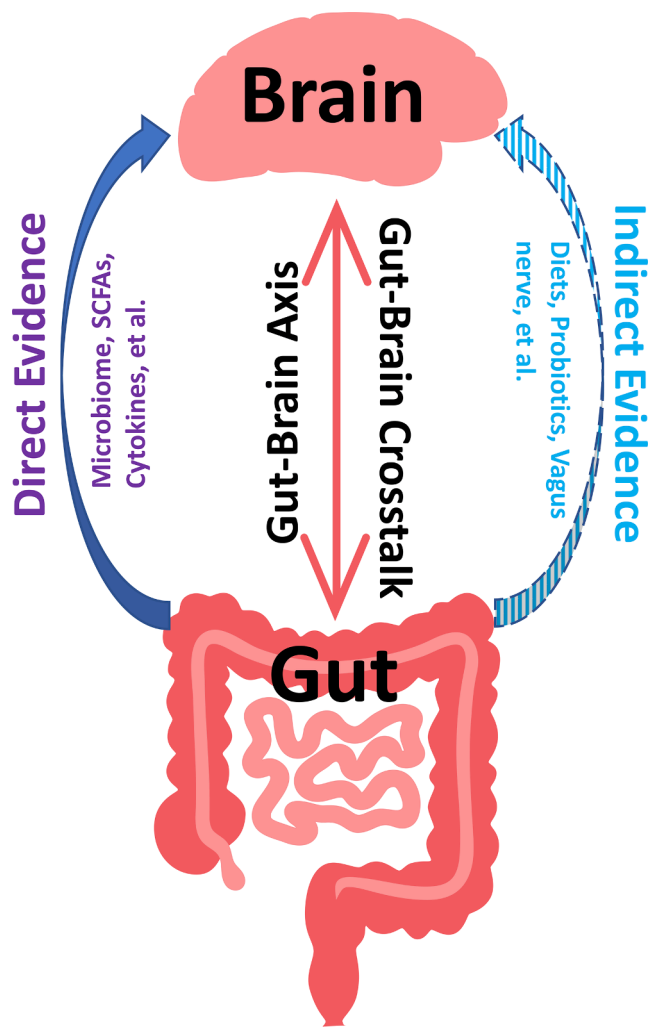
Fig. 1. Potential mechanisms by which gut microbiota is involved in migraine. Gut microbiome can mediate gut-brain crosstalk to contribute to neurological disorders including migraine. Recent studies have provided direct and indirect evidence to demonstrate that gut microbiota plays a critical role in the pathogenesis of migraine. For direct evidence, changes in gut microbiome composition and relevant metabolites SCFAs as well as release of cytokines (such as TNFα) can regulate migraine-like pain in animal models. On the other hand, indirect evidence from previous studies using special diets, probiotics, and vagus nerve stimulation has also suggested that gut microbiota could be targeted to develop a microbiome-based novel therapy for migraine.

(Sp5C) of wild-type mice. Using germ-free (GF) mice and fecal microbiota transplantation (FMT), we further observed that gut microbiota deprivation dramatically prolonged the NTG-induced migraine-like pain and gut colonization with FMT robustly reversed the pain prolongation in the GF mice. Moreover, our results showed that genetic deletion of TNFα or its receptor antagonism significantly inhibited antibiotic treatment-caused migraine-like pain prolongation. Taken together, our study suggests that gut microbiota perturbation may contribute to the pathogenesis of migraine through regulating TNFα signaling in the trigeminal nociceptive system.

In another recent study (Kang et al. 2021), Kang et al. observed that NTG decreased mechanical threshold in mouse hind-paw and differentially regulated the expressions of c-Fos, calcitonin gene-related peptide (CGRP) and TNFα in the Sp5C. They also observed increased basal sensitivity and upregulated trigeminal TNFα expression in GF mice or antibiotics-treated mice compared to specific pathogen-free (SPF) mice. More importantly, this study showed that GF mice colonized with gut microbiota from a migraine patient displayed more severe NTG-induced migraine-like pain than that in the mice receiving gut microbiota from a matched healthy control. Their findings suggest that gut microbiota could be involved in normal mechanical pain sensation and pathological migraine pain.

Wen and co-workers also evaluated the effects of gut microbiota composition on NTG-induced chronic migraine pain in rats (Wen et al. 2019). They found that chronic administration of NTG caused a significant decrease in thermal withdrawal threshold and changes in the microbiota and relevant metabolite production. Their 16S RNA sequencing data showed that 30 bacterial species were altered in the NTG-treated group. Of these, a special interest may be paid to an increase in *Prevotella_1*, which in a clinical study was found to be elevated in women with anxiety and pain (Tillisch et al. 2017). A decrease in *Coprococcus* bacteria in the NTG group was also found to be clinically relevant in humans and linked to increased feelings of depression (Valles-Colomer et al. 2019). Wen et. al. found that treatment of the NTG group with a pair of traditional Chinese medicines, *Gastrodia elata Blume* and *Uncaria rhynchophylla* was able to recover the bacteria near control animal levels as well as elicit similar pain relief as treatment with sumatriptan, a commonly used anti-migraine medication.

Lanza et al. also used the NTG mouse model to investigate the relationship between gut microbiota and migraine (Lanza et al. 2021). They evaluated the effects of administration of short-chain fatty acids (SCFAs) on NTG-induced migraine-like pain and gut function. SCFAs are the metabolite products of bacteria in the GI tract and are involved in a host of local and systemic effects, such as glucose homeostasis, satiety, anti-inflammatory action, and brain signaling. Microbiota composition is directly related to production of SCFAs as each class of bacteria produces only 1 or 2 SCFAs. The SCFAs used in this study are mainly produced in the gut by *Bacteroidetes* and *Firmicutes*. They found that treatment with SCFAs reduced NTG-induced hyperalgesia in the tail flick test and formalin challenge test. They also found that SCFA treatment resulted in less release of proinflammatory cytokines TNFα and IL1-β in the intestine after NTG injection. Interestingly, such SCFA treatment can reduce inflammation in the gut, which will result in less intestinal wall damage and prevent NTG-caused loss of neurons in the trigeminal nucleus. The results from this study suggest that SCFAs could be used as a novel therapy for migraine and relevant intestinal disorders.

Moreover, Chen et al examined the microbial differences between elderly women who suffered from migraine and migraine-free controls (Chen et al. 2019). The migraine group showed lower levels of alpha diversity when compared to adults without migraine. It has been demonstrated that alpha diversity, the amount of different bacterial species within a sample, is an indicator of general gut health and has been linked to several disorders (Hagerty et al. 2020). It was found from fecal samples of over 100 women that the migraine group also had less butyrate-producing bacteria and overall fewer bacteria thought to be beneficial. They then performed pathway analysis on the groups and found that the kynurenine degradation pathway, the glutamate degradation pathway, and the gamma-aminobutyric acid (GABA) synthesis pathway were enriched in the migraine group. In addition, metabolic pathways were less abundant in the migraine group. These data indicate that the migraine group may have altered metabolism and neurotransmission when compared to the controls.

Indirect evidence of gut microbiota involved in migraine

Diet is a key regulator of gut microbiota (David et al. 2014; Singh et al. 2017; Wu et al. 2011). Diet changes could explain over 50% of variation in gut microbiota compared to genetic alterations which only explained approximately 10% of variation (Zhang et al. 2010). As noted by Peatfield, dietary foods have been a long-known factor in triggering migraine (Peatfield et al. 1984). Based on this foundation, numerous dietary interventions have been studied for their efficacy in migraine treatment. The most well studied of these is the ketogenic diet. The ketogenic diet is a high fat, low carbohydrate, moderate protein diet that

shifts the body metabolism from using glucose as its main energy source to fatty acids (Paoli et al. 2013). The lack of glucose availability causes the liver to produce ketone bodies from fatty acids which enter the bloodstream and are taken up by different cells including those in the central nervous system. Cellular oxidation of ketone bodies produces acetyl-CoA which is then used in the Krebs cycle to generate ATP (Dąbek et al. 2020). In addition to being used for energy production, ketone bodies are involved in a wide array of cellular signaling, including epigenetic changes and alterations of dopamine, serotonin turnover, and GABA uptake (Calderón et al. 2017; Dahlin et al. 2012; Ruan and Crawford 2018). The ketogenic diet is also known to alter gut microbiota (Newell et al. 2016). A study of 96 females with migraine on a ketogenic diet showed a decrease in attack frequency, number of days with headache, and medication intake starting at 1 month after switching to the ketogenic diet that continued the improvement throughout the 6 month study (Di Lorenzo et al. 2015). A case report also showed a decrease in migraine frequency following a ketogenic diet and noted that the therapeutic effect of the ketogenic diet on migraine continued after cessation of the diet (Strahlman 2006). In a randomized placebo-controlled trial, Ramsden et al. assessed the effect of dietary intervention that provides increased n-3 fatty acids with and without reducing n-6 linoleic fatty acids (Ramsden et al. 2021). The data from this trial showed that both interventions caused a reduction in headache frequency and severity (Ramsden et al. 2021). Their previous study indicates that these dietary interventions cause an increase in n-3 fatty acid derived endocannabinoids with a reduction in n-6 fatty acid derived endocannabinoids (Ramsden et al. 2015). This is an intriguing finding as altered endocannabinoid signaling has been found in patients with chronic migraine (Greco et al. 2018).

Probiotics are another potential therapy for migraine, which like dietary interventions are able to alter the gut microbiota (Hemarajata and Versalovic 2013). In the NTG-induced migraine mouse model, we found that oral gavage of a probiotic mixture significantly inhibited migraine-like pain prolongation caused by antibiotic treatment (Tang et al. 2020). A randomized placebo-controlled trial by de Roos and colleagues showed that in 63 migraine patients, there was no benefit achieved over a 3-month trial of probiotic supplementation compared to a placebo group (de Roos et al. 2017). However, in a randomized double-blind controlled trial, Martami et al. observed that in 40 episodic and 39 chronic migraine patients, an 8-week trial of probiotics significantly decreased migraine severity, frequency, and medication use when compared to placebo controls (Martami et al. 2019). The inconsistency found in the two randomized clinical trials may be due to different strains of probiotics used in the two studies (de Roos et al. 2017; Martami et al. 2019).

Cortical spreading depression (CSD) is characterized by a wave of excitation followed by inhibition in brain neurons that propagates slowly throughout the brain (Charles and Baca 2013; Close et al. 2019; Somjen 2001; Takizawa et al. 2020). CSD is thought to be the mechanism by which migraine aura occurs (Lauritzen 1994). CSD may also be a triggering event for migraine attacks without aura (Ayata 2010). The vagus nerve is a key communication point between gut and brain and can regulate the effect of altered microbiota composition on brain activity and function, and it is clear from animal and human studies that vagus nerve signaling is involved in migraine pathogenesis (Bonaz et al. 2018; Liu and Forsythe 2021; McVey Neufeld et al. 2019; Zhang et al. 2020b). The Ayata group has investigated the role of the vagus nerve in CSD (Chen et al. 2016; Morais et al. 2020). They observed that activation of vagus nerve afferent sensory fibers to the nucleus tractus solitarius (NTS) mediated CSD suppression. They also found that projections from NTS to locus coeruleus and dorsal raphe nucleus released norepinephrine and serotonin, which are critical mediators for vagus nerve suppression of CSD. Using vagus nerve stimulation, previous studies have revealed that such stimulation can directly inhibit migraine pain in both migraine animal models and migraine patients (Hawkins et al. 2017; Martelletti et al. 2018).

Future research perspectives

The studies into the role of gut microbiota in migraine have resulted in a deeper understanding of the pathophysiology of migraine and exciting new avenues to be explored for new therapies. However, further studies for determining the exact microbiome changes that cause migraine are of critical need. Understanding these changes may lead to personalization of microbiome-based non-opioid migraine treatments, such as dietary interventions or microbiome metabolites supplementation. An added benefit to these treatments is their low cost compared with traditional pharmaceutical drugs or antibody infusions. It is important to note that further studies into the role of the gut microbiota on migraine also need to be done in different animal models of migraine. Future microbiome studies using validated models such as genetic models would greatly enhance our understanding of migraine pathogenesis (Ayata et al. 2006; Parker et al. 2021; Spekker et al. 2021). Previous studies have shown that both facial and hindpaw hypersensitivities as well as photophobia are displayed in NTG-induced migraine rodent models. Even though limb pain has been reported in migraineurs (Angus-Leppan and Guiloff 2016; Guiloff and Fruns 1988; Prakash et al. 2009), cephalic pain is the typical symptom of patients with migraine. Thus, more studies are needed to demonstrate whether hindpaw hypersensitivity can be used as an indicator for migraine pain. Additionally, a better understanding of how altered gut microbiome composition affects vagus nerve signaling will allow for better targeted vagus nerve modulation to develop a novel therapy for migraine. Such low-risk non-invasive treatment would be of real benefit to migraine patients.

Conclusion

A body of evidence has come out in recent years linking the gut microbiota and migraine. Studies using animal models and human studies have demonstrated that the gut microbiome is altered in migraine sufferers compared to healthy controls. Previous studies have also shown a beneficial effect of a multitude of different treatments that target the gut microbiota and vagus nerve signaling, such as special diets, probiotics, and vagus nerve stimulation. These exciting findings leave a number of important mechanistic questions to be explored in the future but open up the possibilities of developing personalized microbiome-based migraine therapies.

Author contributions

JC and FT conceived the study. JC collected information, and JC and SL contributed to data interpretation. JC wrote the draft of the manuscript and FT revised the manuscript. All authors reviewed and provided critical feedback for the final manuscript.

Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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