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EPISODIC MIGRAINE (R COWAN, SECTION EDITOR)

What the Gut Can Teach Us About Migraine

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Abstract During gestation, cells of the brain and gut develop almost simultaneously into the central nervous system (CNS) and enteric nervous system (ENS), respectively. They remain connected via the vagal nerve lifelong. While it is well known that the brain sends signal to the gut, communication is in fact bidirectional. Just as the brain can modulate gut functioning, the gut, and likely what we ingest, can in fact influence our brain functioning. We will first review both gastrointestinal (GI) function and migraine pathophysiology and then discuss evidence linking the migraine brain to various GI disorders. Lastly, we discuss the effects of gut microbiota on brain functioning and speculate how the gut and particularly diet may affect migraine.

Keywords Migraine · Gastric stasis · Autonomic dysfunction · Gut microbiota · Probiotics

Introduction: the Gut and Migraine

As a common and disabling primary headache disorder, migraine affects roughly 18 % of women and 6 % of men [1]. Migraine is defined by the International Classification of Headache Disorders, 3rd edition, beta version as a recurrent disorder with moderate to severe headache attacks lasting 4–72 h with associated features including nausea and/or vomiting [2].

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Migraine is often accompanied by other gastrointestinal (GI) symptoms including diarrhea, constipation, and dyspepsia and has been associated with GI conditions such as gastric stasis, gastroesophageal reflux (GERD), irritable bowel syndrome (IBS), and celiac disease [3–6].

In a series of 500 migraine patients completed in 1960, Selby and Lance reported 87 % of migraineurs experienced associated nausea and 56 % experienced vomiting [7].

More recently epidemiological studies based on data from the American Migraine Study report similar findings; 73 % of migraineurs have associated nausea, and 29 % note associated vomiting. Similarly, in 2012, Lipton and colleagues reported data from the American Migraine Prevalence and Prevention Study (AMPP) with 49.5 % of episodic migraine patients identifying associated high-frequency nausea with their headaches and 29.1 % describing low-frequency nausea [8].

Gastric stasis, or gastroparesis, is characterized by delayed gastric emptying in the absence of mechanical obstruction in the proximal GI tract with typical symptoms including nausea, vomiting, bloating, early satiety, abdominal discomfort, and weight loss [9]. Gastric stasis is estimated to affect five million persons in the USA with a largely female predominance [10, 11]. The most common etiologies are diabetes mellitus in 30 % and postsurgical causes in 19 %, and 36 % remained idiopathic [12].

Much like the International Headache Society criteria for migraine, the Rome III Criteria was developed by expert consensus for diagnosis of GI disorders. Although the diagnosis of dyspepsia remains vague, the Rome III Criteria defines functional dyspepsia as a symptom of epigastric pain or discomfort, postprandial fullness, and early satiety within the last 3 months. A study conducted in 2006 evaluated the prevalence of upper abdominal symptoms in migraineurs, defining dyspepsia as pain centered in the upper abdomen. Using a validated tool, The Bowel Disease Questionnaire, 81 % of

migraineurs reported dyspepsia compared to 38 % of healthy controls [3].

Described by the Rome III criteria as a functional bowel disorder consisting of recurrent episodes of abdominal pain or discomfort and marked changes in bowel habits, IBS shares many similar characteristics to migraine [6]. The prevalence of IBS in the USA is estimated at 14 %, and analogous to migraine, has a female predominance, frequent family history, fluctuation in natural disease course, association with triggers, and psychiatric comorbidity [6, 13]. A recent literature review estimated the risk of IBS subjects to have coexisting migraine was 25–50 % compared to 4–19 % in controls estimating an odds ratio of 2.66 [14].

Celiac disease (CD) is an autoimmune disorder characterized by sensitivity to gluten leading to an immune response in the gut that can lead to villous atrophy and classic presentation of diarrhea and symptoms of malabsorption [15]. Diagnosis is verified through serology and intestinal biopsy. When biopsy fails to be diagnostic, yet removal of dietary gluten improves symptoms, the disorder is gluten sensitivity (GS), which has increasing public attention. Both CD and GS have been associated with migraine with a recent study assessing the prevalence of migraine using a self-administered survey in patients with CD, GS, and IBD. Chronic headaches were reported by 30 % of CD, 56 % of GS, 23 % of IBD, and 14 % of controls and migraines in 40 % of GS and 21 % of CD, all significantly higher than controls [16].

Gut Pathophysiology

Neurogastroenterology encompasses control of digestion through interplay of the enteric nervous system (ENS), central nervous system (CNS), and the sympathetic ganglia of the autonomic nervous system (ANS) [17]. Like the brain and spinal cord, the ENS is derived from neural crest cells and secretes similar neurotransmitters including acetylcholine, dopamine, serotonin, and calcitonin gene-related peptide (CGRP) [18]. The ENS, often referred to as the "second brain," arises from precursor cells that migrate from the neural crest along the vagus nerve to inhabit and differentiate in the gut. It contains between 200 and 600 million neurons, paralleling the number in the spinal cord [19].

Gastric emptying and motility are facilitated by interaction between smooth muscles, the ENS, CNS, the ANS via the sympathetic ganglia, and the interstitial cell of Cajal (ICC) where sympathetic activation leads to inhibition of gut peristalsis [20].

Moreover, sensory information from the GI tract is transmitted through vagal afferent neurons via glutamatergic synapses to terminate in the nucleus tractus solitaries (NTS). Here, second-order neurons integrate synaptic inputs from vagal afferent neurons as well as higher CNS centers involved in autonomic regulation including the caudal ventrolateral medulla (CVLM) and the paraventricular nucleus of the hypothalamus (PVN) [21–23]. Among other areas, the NTS projects to the adjacent dorsal motor nucleus of the vagus (DMV) using primarily glutamate, GABA, or norepinephrine as neurotransmitters. These neurons are preganglionic parasympathetic providing the vagal motor output to the GI tract where they release acetylcholine onto postganglionic neurons located within target organs. In the stomach, postganglionic parasympathetic neurons are either excitatory and cholinergic, increasing gastric tone, motility, and secretion, or inhibitory, non-adrenergic, and non-cholinergic (NANC), inhibiting gastric function via release of nitric oxide (NO) or vasoactive intestinal polypeptide (VIP).

Vagal nerve dysfunction has been implicated in the etiology of gastric stasis. Animal studies demonstrate pyloric relaxation induced by gastric distension is significantly reduced by subdiaphragmatic vagotomy, thereby prohibiting food passage [24]. Furthermore, demyelinating disease in the medullary region of the brainstem, presumably the vagal nerve nuclei, secondary to multiple sclerosis, has been correlated with gastroparesis and abnormal gastric emptying studies [25].

Additionally, recent evidence supports the idea that intestinal microbiota can have dramatic effects on the development and function of the brain possibly via the vagal nerve. The intestinal surface contains 100 trillion microorganisms, the largest population of commensal microorganisms of all body surfaces, and within the gut-associated lymphoid tissue houses 70–80 % of the body's immune cells. One layer of columnar intestinal epithelial cells separates the host from this complex microbial environment [26]. Adjacent to the mucosal immune cells are subsets of vagal afferents containing receptors for signaling molecules released from the cells including mast cell products and cytokines. Vagal afferents project to the NTS, as previously described, and a complex system of cortical and subcortical structures. Cortical regions including the medial prefrontal cortex and the anterior cingulate cortex project to subcortical areas including the periaqueductal gray (PAG) and the medullary vagal complex. This integrated system thus modulates motor autonomic, neuroendocrine, and pain modulatory components between the gut and the brain [27, 28].

Migraine Pathophysiology

The pathophysiology of migraine is complex involving several brain regions, pathways, and neurotransmitters. Whether headache pain originates from the cortex or the brainstem or via activation of peripheral nociceptors remains under debate.

There is evidence supporting the onset of the headache phase depends on nociceptive input from the perivascular sensory nerve terminals with trigeminal fibers on extracranial, dural, and pial arteries all playing a role [29]. Neurogenic

inflammation of the dura involves the release of various vasoactive peptides from parasympathetic perivascular and trigeminal fibers including calcitonin gene-related peptide (CGRP), substance P, and neurokinin A. These peptides in turn stimulate a sequence of events leading to vasodilatation, plasma protein extravasation, and the release of pro-inflammatory mediators. Mediators including prostanoids, free radicals, kinins, protons, cytokines, and the complement system activate trigeminal afferents [30]. Sensory afferents via the trigeminal tract then pass caudally to converge onto the spinal trigeminal nucleus [31].

Likewise, there are studies suggesting that not only the prodromal phase of migraine but also the headache phase itself originates centrally secondary to increased cortical responsiveness [32–34]. Furthermore, cortical spreading depression (CSD), the pathophysiological correlate of migraine aura, can activate the trigeminovascular system [35].

Prodromal migraine symptoms such as irritability, sleepiness, fatigue, nausea, and loss of appetite appearing before the onset of the headache are thought to be related to abnormal neuronal activity in the cortex, diencephalon, or brainstem. The hypothalamus, which plays a central role in autonomic function, has been implicated in premonitory migraine symptoms [36]. On the other hand, symptoms emerging after the onset of migraine are thought to be related to the influx of intracranial pain signals originating in the meninges to supramedullary brain structures involved in sensory, autonomic, affective, and endocrine functions. This nociceptive information then converges onto the spinal trigeminal nucleus with further projections to various brain areas including the hypothalamus and thalamus. Furthermore, an area with the most second-order trigeminovascular neurons, the ventrolateral area of the upper cervical and medullary dorsal horn, projects to the periaqueductal gray matter (PAG), rostral trigeminal spinal nuclei, the NTS, brainstem reticular areas, superior salivatory nuclei, and the cuneiform nuclei [37•]. Hypothalamic activation for the first time, alongside activation of the midbrain and pons, was reported using positron emission tomography (PET) imaging of seven migraineurs during spontaneous attacks [38]. This suggests interplay between the hypothalamus, PAG, and ventral tegmental area in regulating autonomic and pain components of migraine [39].

Several studies provide evidence for autonomic dysfunction in migraine. Autonomic symptoms commonly include nausea, vomiting, diarrhea, cutaneous vasoconstriction, vasodilation, piloerection, and diaphoresis. A population-based case-control study of migraine during the headache-free period showed that compared with controls and non-disabled migraineurs, resting diastolic blood pressure was higher and pulse rate variation was significantly lower in disabled migraineurs [40]. A recent study measured heart rate variability, skin temperature, skin conductance, and respiration in headache patients, with results suggesting both sympathetic hyperfunction and parasympathetic hypofunction in this population [41]. Previous studies reported similar findings of sympathetic hypofunction in migraine and tension-type headache [41–44], whereas other studies have reported sympathetic hyperfunction in migraineurs [41]. In a recent pediatric study, among 202 migraineurs, 55 % reported associated autonomic symptoms, which were significantly more frequent than in other primary headache disorders. Most commonly reported was red ear and facial flushing among 21 % each, conjunctival injection in 18 %, and lacrimation in 17 % [45]. This study also reported that migraineurs with cranial autonomic symptoms reported more frequent general autonomic symptoms: vasomotor in 56 % and GI dysfunction such as abdominal pain, cramping, early satiety, and persistent fullness in 42 %.

The Brain-Gut Connection

The ANS is implicated in the generation of migraine and GI dysfunction with evidence for overlapping symptoms in both domains such as nausea, vomiting, dyspepsia, IBS, and gastric stasis. The ANS may also be the link between alterations in brain function and behavior secondary to intestinal flora dysbiosis.

Migraine and GI Disorders

Nausea during migraine was assumed to be secondary to gastric stasis. However, studies by Aurora and colleagues suggest that nausea is caused by a central brainstem process, and not by gastroparesis, as stasis is present outside of migraine attack [46]. The pathophysiology of nausea is complex involving GI motor and sensory disturbance, autonomic dysfunction, and central nervous system regulation. It is postulated to include the hypothalamus and the inferior cortical gyrus [47, 48]. A recent retrospective study reported a high prevalence of comorbid conditions in children with chronic nausea including migraine, autonomic disturbances, sleep disturbance, anxiety, and fatigue [49]. Nausea was also the only individual symptom statistically associated with delayed gastric emptying in 50 children studied [50]. Recent functional MRI findings suggest increasing phasic activity in the amygdala, putamen, and dorsal pons/locus coeruleus preceding nausea with increasing sustained response with increased nausea with activation of the insular, anterior cingulate, orbitofrontal, somatosensory, and prefrontal cortices [51].

There is better understanding of the brain structures involved in emesis that lie within the dorsal vagal complex of the medulla. Comprised of the NTS, DMV, and the area postrema [52], DMV activation stimulates vagal and sympathetic efferent pathways to the GI tract and within the spinal nerves to the diaphragm and abdominal muscles [23].

Gastric stasis has long been implicated in association with migraine. Early experimental studies by Volans et al. reported a delay in effervescent aspirin absorption in 19 out of 42 migraineurs during an attack, but not during the headache-free period and not found replicated in patients with tension-type headache [53, 54]. More recent studies suggest delayed gastric emptying occurs during spontaneous migraine attacks, visually induced migraines, and during the headache-free interictal period [4, 46, 55]. Using gastric scintigraphy, the rate of gastric emptying was measured in 10 migraineurs and 10 age- and sex-matched controls. The time of half emptying after an induced migraine attack was delayed 78 % ictally and 80 % interictally in migraineurs, and compared to non-migraine controls, the time of half emptying was significantly longer at 188.8 min compared to 111.8 min. Subsequently, Aurora and colleagues confirmed findings of delayed half emptying during spontaneous migraine attacks as well. Another study found contradictory results in migraineurs without interictal dyspepsia symptoms. Compared to migraineurs, subject with FD had more delayed gastric emptying [56]. However, a study evaluating liquid-phase gastric emptying observed delayed ictal but not interictal gastric emptying in migraineurs compared to controls [57].

Cyclic vomiting syndrome (CVS), characterized by recurrent episodes of nausea, vomiting often with associated abdominal pain and diarrhea, has been seen in both pediatric and adult populations. Personal and/or family history of migraine was noted in 39–82 % of children and 24–70 % of adults with CVS [58–60]. In both CVS and migraine, sympathetic adrenergic dysfunction as defined by vasoconstriction to cold and vagal cholinergic dysfunction evidenced by lower Valsalva ratio and ECG R-R interval were observed [61]. Likewise, the pediatric CVS population has been found to have increased sympathetic modulation of the sinus node and abnormal sudomotor testing suggesting sympathetic impairment in both vasomotor and sudomotor pathways [48, 62]. A study investigating cyclical symptoms in diabetic adults with gastroparesis found a higher percentage of migraines and delayed gastric emptying in those with cyclical vomiting patterns [63]. Furthermore, autonomic nerve dysfunction was found in 43 % of adult CVS patients with sympathetic abnormalities predominating [64]. CVS is theorized to be a "brain-gut disorder" mediated by the neuroendocrine system where corticotropin-releasing factor (CRF) is released from the hypothalamus as a reaction to stress. CRF then acts to inhibit the DMV, thus triggering nausea and delayed gastric emptying [65].

Furthermore, IBS has been associated with migraine. IBS has been hypothesized to stem from hyperactive amygdala activity and has been associated with decreased gray matter density throughout the brain and morphological white matter changes in regions implicated in the pain matrix [66–68]. A recent population-based retrospective cohort study in Taiwan found that the incidence of IBS was 1.95-fold higher in the migraine cohort than non-migraineurs. This was particularly evident in the cohort of migraineurs younger than 30 years old, who exhibited a 3.36-fold increased risk of IBS [69]. It is theorized that the underlying pathophysiology of IBS and migraine is a genetically established hypersensitive or hyperexcitable brain. Environmental, psychological, and immunological factors may increase sensitization in the ENS and brain-gut axis in IBS [6]. A recent case report described a young man with severe attacks of IBS symptoms occurring in discrete 2–8-week clusters for periods of 30–120 min, a semiology parallel to cluster headache. This further suggests the importance of the hypothalamus as a pathophysiological link between these disorders [70].

Gut Microbiota and Brain Function

The comparison of germ-free animals with those colonized with a single or multiple strains of bacteria has commonly been used to investigate the interaction between the host and the microbiota. Likewise, probiotics, microbial bacteria, or yeast that, in sufficient quantities, convey health benefits to the host are utilized in these investigations. Disruption or dysbiosis of the symbiotic relationship between the GI microbiota and the host impedes mucosal immune function, motility, epithelial barrier integrity, and absorption of nutrients with possible implications in GI and CNS disease.

In mice, perturbation of commensal GI bacteria with antibiotics leads to reduction in the *Lactobacillus* population, elevation in myeloperoxidase activity, and substance P in the intestinal wall with functional consequence of increased visceromotor or pseudoaffective response, a response profile suggestive of IBS [71, 72]. Mice gavaged with *Lactobacillus paracasei* showed improvement in antibiotic-induced changes in inflammation, neurotransmitter content, and visceromotor response.

Modulation of gene expression for nutrient absorption regulation, mucosal barrier enhancement, and angiogenesis has been demonstrated in comparison with germ-free mice and mice colonized with *Bacteroides thetaiotaomicron*. Colonization with this bacteria also induced an increase in mRNA encoding of the synaptic vesicle-associated protein-33 which is involved in synaptic neurotransmission [73, 74].

Furthermore, the influence of the gut on brain function and behavior has been demonstrated in models of stress, depression, anxiety, and autism. Maternal separation in infant rhesus monkeys leads to a reduction in lactobacilli and the emergence of enteric pathogens such as *Campylobacter jejuni* [75]. Similarly, studies simulating stress induction via maternal separation of rat pups show increase in stress response, cytokine response, intestinal permeability, and a shift in GI tract bacterial composition [76].

In a rat model of depression, those given *Bifidobacteria infantis* for 14 days exhibited increased plasma levels of tryptophan, the precursor of serotonin, suggesting its possible

antidepressant effects [77]. Perhaps the most robust data comprises experimental studies of anxiety. Decreased anxiety has been reported in germ-free mice compared to specific pathogen free (SPF) mice [78••, 79, 80]. Likewise, probiotics have been reported to have a significant effect anxiety like behavior. Infection with *Trichuris murins* induced anxiety like behavior that was reversed with *Lactobacillus rhamnosus* NCC4007 and *Bifidobacterium longum* NCC3001 treatment [81]. Another study reported the use of probiotics *Lactobacillus helveticus* R0052 and *B. longum* R007 had anxiolytic effects compared to placebo in rats [82]. Likewise, mice infected with *Citrobacter rodentium* displayed increased anxiety [83].

A developing area of interest is largely focused on the role of the microbiota in autism spectrum disorders, as GI disturbance is prevalent in children with autism and several studies demonstrate alterations in the microbiota in children with autism [84]. In comparing autism patients with controls, biopsy samples from those with autism showed a reduction in *Bifidobacterium* spp. and the mucolytic bacterium *Akkermansia muciniphila*. The latter species is thought to influence bacterial translocation and foster gut dysfunction [85]. One study observed a significant increase in *Bacteroidetes* in autism patients, whereas *Firmicutes* were higher in control patients [86]. In contrast, another study found reduced *Bacteroidetes* and increased *Firmicutes* and *Betaproteobacteria* (Sutturela) in autism patients with GI disturbances compared to patients with GI disturbances alone. This microbiota is associated with reduced ileal transcripts encoding disaccharidases and hexose transporters suggesting carbohydrate malabsorption, a shift in luminal substrates availability for microorganisms and possibly prompting dysbiosis. This theory is further supported by a study reporting apparent benefit from the use of oral vancomycin in some patients with autism [87, 88].

To better ascertain changes in brain function in humans as influenced by the gut, Tillisch et al. acquired evoked and resting-state brain responses using functional magnetic imaging (fMRI) in healthy women before and after a 4-week consumption of fermented milk product containing probiotic (FMPP). This specific FMPP containing *Bifidobacterium animalis* subsp. *lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *Lactococcus lactis* subsp. *lactis* was chosen due to evidence supporting GI benefits in healthy patients and those with IBS and reduction in reflex responses to noxious visceral stimuli. The imaging paradigm incorporated a task engaging affective, attentional, sensory, and integrative brain regions likely involved in potentially life-threatening or negative situations. FMPP ingestion was associated with reduction in activity in brain regions involved in a sensory brain network including the primary interoceptive and somatosensory cortices; precuneus, frontal prefrontal temporal cortices; parahippocampal gyrus; and the PAG. Resting-state changes within the PAG network were also noted with FMPP intervention. It is possible that these changes may be related to modulation of ascending monoamingergic system via the vagal nerve activity to the PAG after signaling in the NTS or possibly FMPP alteration of systemic metabolism [89].

Conclusions and Implications

The physiological connection between the gut and the brain as well as the influence on brain function and behavior has been well established. Inflammation at the level of the trigeminovascular system is hypothesized to play a role in migraine pathophysiology and could be influenced by inflammation and immune modulation in the GI tract and systemically as evidenced by recent studies [90, 91]. Likewise, there is evidence to suggest that the gut microbiota plays an important role in the brain-gut axis and aberrancies may be associated with neurological disease like migraine.

The influence of the immune system on migraine has long been debated. A recent study evaluated various immune markers in three patient populations: those with chronic migraine (CM) with medication overuse headache (MOH), healthy controls, and episodic migraine (EM) with aura. WBC and lymphocytes, as well as CD3, CD4, CD8, and CD19 were significantly elevated in CM with MOH patients compared to EM and healthy controls (HC). While beta endorphin levels were significantly lower in CM compared to HC with EM displaying an intermediate value [92].

A double-blind, randomized controlled, crossover clinical trial by Aydinlar et al. evaluated the impact of an elimination diet on 21 migraineurs with IBS. They tested IgG antibody titers to 270 food allergens, and during a 6-week diet phase, participants were either allocated to an elimination or provocation diet and were crossed over for an additional 6 weeks. There was a resultant significant improvement in both migraine attack counts, duration, maximum severity, and acute medication used as well as IBS parameters. They theorize that the increase in IgG antibodies and cytokines via food allergy antigens results in inflammation as a possible component underlying migraine pathophysiology [93••].

Recent studies also suggest dietary supplementation has beneficial effects on migraine. One open-label study reported improvement in quality of life in migraineurs after using two nutritional formulations for 90 days. Combination A contained enzymatically rendered fish protein high in bioactive peptides and amino acids, four probiotics (*Lactobacillus acidophilus*, *L. bulgaricus*, *Enterococcus faecium*, and *Bifidobacterium bifidum*) and chlorophyll, whereas combination B, including 21 different ingredients was designed to improve the nutritional status of the kidneys and liver. This supports the theory of migraine in part stemming from underlying dysbiosis and dysfunction of normal body absorption and assimilation of nutrients [94].

Likewise, nutritional modifications have been investigated in migraine treatment.

As major constituents of vascular, immune, myelin, glial, and neuronal cell membranes, omega-3 (*n*-3) and omega-6 (*n*-6) polyunsaturated fatty acids (PUFA) can be transformed into lipid mediators associated in pain processing. In general, those derived from *n*-6 fatty acids have pronociceptive properties while those from *n*-3 derivatives are antinociceptive. In a dietary model involving *n*-3 and *n*-6 PUFAs, Ramsden et al. compared chronic headache patients given a low *n*-6/high *n*-3 diet to a low *n*-6 PUFA diet. Patients in the high *n*-3 and low *n*-6 group showed significant improvement in HIT-6 scores, number of headache days per month, headache hours per day, and greater increase in antinociceptive *n*-3 pathway markers [95].

Furthermore, Bunner et al. investigated the use of a low-fat vegan diet in migraine. In this crossover study, participants were assigned to a low-fat vegan diet for 4 weeks followed by an elimination diet or a dietary placebo supplement and crossed over after 16 weeks with a 4-week washout period. The vegan diet was associated with reduction in reported pain compared to the supplement period. It is thought that the role of neurogenic inflammation in migraine may be reduced by a vegan diet as many plant foods are high in anti-inflammatory compounds and antioxidants and likewise meat products have been reported to have inflammatory properties [96].

Overall, evidence suggests alterations in gut microbiota based on dietary changes, and possibly, inflammation reduction can have a significant impact not only on GI and brain function and development but as a mediator in migraine. Further research is warranted in targeting various probiotics and anti-inflammatory pathways and their clinical efficacy and impact in migraineurs.

Compliance with Ethics Guidelines

Conflict of Interest Nada Hindiyeh and Sheena K. Aurora each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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