Migraine, the Gut, and the Brain 2022

Stephen D Silberstein, MD
Jefferson Headache Center
Thomas Jefferson University Hospital
Philadelphia, PA
Brain

Front View

Cerebral cortex

Brainstem

Side View

Cerebellum
Brain Facts

- Sperm Whales: have largest brain 17 lbs, human brain 3 lbs
  - Neanderthal brains 10% larger
- Brain is 2% of your body weight but uses 20% of its energy
  - Brain is 73% water
  - Brain tissue size of a grain of sand contains 100,000 neurons and one billion synapses
  - Each neuron can transmit 1000 nerve impulses per second
  - Supercomputers can only achieve small fraction of the human brains power
Gut
Gut Facts

- 30 feet long: mouth to anus
- Has its own enteric nervous system: second brain
- When vagus nerve cut it continues to operate
- 90% of vagus nerve input is from gut to brain
- 95% of total serotonin and 50% of dopamine in gut
- Gut microbes can digest food that we cannot
Brain/cloud

Internet/Vagus/Sympathetics

Laptop/Gut/Second Brain
Two Neural Pathways Transmit Information to CNS

- Sympathetic
- Vagal

Both: Cell Bodies outside gut [Extrinsic (EXPAN)]

- Sympathetic in thoracolumbar and lumbosacral dorsal root ganglia (DRGs)
- Vagal in nodose and superior (jugular) ganglia of vagus nerve
  - Projects to nucleus of solitary tract (NTS) and area postrema

Cell bodies in gut [Intrinsic Neurons (IPAN)]

- Provide sensory information
- Lie within submucosal and myenteric plexuses of gut wall

Gershon and Margolis J Clin Invest. 2021;131(18)
Gut signaling

- Bowel pain and discomfort (e.g., bloating and urgency) detected by sympathetic nerves

- Nutrient composition and gastric volume transmitted to CNS by Vagus nerve
  - Can result in satiety and/or nausea

- Vagal afferents sense microbe-associated molecular patterns (MAMPs)
  - Keeps GI tract microenvironment under strict brain surveillance

Gershon and Margolis J Clin Invest. 2021;131(18)
The Intestinal Microbiome (Bacteria)

- Contributes to regulation of GI motility and mood
- Gut microbiome, its enteric container, and associated pathways to brain CALLED “gut connectome”
- Communicates with CNS through neuronal, endocrine, and immune signaling
- CNS can impact gut microbiota, via stress mediator and sympathetic and parasympathetic control of GI motility, secretion, and immunity

Gershon and Margolis J Clin Invest. 2021;131(18)
Bacterial Antigen Promotes Intestinal Homeostasis

In mice a conserved epitope in the Bacteroidetes enzyme b-hexosaminidase (b-hex) presented by antigen-presenting cells (APCs) to CD4+ cells to drive their differentiation to CD4+CD8aa+ intraepithelial lymphocytes (CD4IELs) in intestinal tissue and forkhead box P3+ (FOXP3+) peripheral regulatory T cells (pTreg cells) in gut-associated lymphoid organs. These two Treg cell populations suppress intestinal inflammation and promote homeostasis.

One antigen can → 2 distinct Treg cells
1) CD8aa+ CD4IELs in intestinal tissue
2) forkhead box P3+ pTreg cells in gut-associated lymphoid organs
The ability of the brain to influence the intestinal microbiota

Gut-brain axis

The ability of the microbiota to influence brain and behavior

Microbiota-gut interplay

GBA
Headache Treatment

Depends on:

• Making an accurate diagnosis
• Ruling out alternative etiologies
• Ordering appropriate studies
• Addressing headache’s impact

Ultimate Goal: Headache Relief

Patients want to know what is wrong and that their complaints are taken seriously
Headache Treatment

Acute (Abortive)
• Taken after attack has begun to relieve pain and disability and stop progression

Preventive
• Taken to reduce attack frequency, severity, and duration
Acute Treatment Principles

• Treat as early as possible
  – Do not wait for escalation

• Use nonpharmacologic treatment
  – Rest
  – Avoid uncomfortable sensory stimuli
  – Cold compresses

• Use acute medications
  – Almost always indicated
  – Match treatment intensity to attack severity
Comorbidities Impact Treatment Choice\textsuperscript{1-3}

Cardiovascular
- Stroke
- Angina/MI
- Raynaud disease
- Hypertension
- Mitral valve prolapse
- Patent foramen ovale (migraine with aura)

Psychiatric
- Bipolar disorder
- Depression
- Generalized anxiety disorder
- Panic disorder

Neurologic
- Epilepsy
- Bell’s palsy?
- Essential tremor
- Fibromyalgia
- Positional vertigo
- Restless legs syndrome

Gastrointestinal
- Irritable bowel syndrome
- Peptic ulcer disease?

Other
- Allergies
- Asthma
- Obesity?

Gastrointestinal Symptoms Complicate Migraine and Its Therapy

- Nausea episodically affects up to 90% of persons with migraine
- Vomiting occurs in up to 50% of persons with migraine
- More than 1/3 of persons with migraine with nausea cannot tolerate oral medications
- Efficacy of oral medications lost if vomiting occurs
- Efficacy of medications reduced due to gastric stasis and delayed absorption

Neurogastroenterology & Motility. 2019;31(Suppl. 2)
Migraine And GI Disorders

- Gastroparesis
- Helicobacter pylori infection
- Irritable bowel syndrome
- Inflammatory bowel disease
- Celiac disease
- Cyclic Vomiting
- Abdominal migraine

Gastroparesis

- Gastroparesis is a chronic motility disorder of the stomach that involves delayed emptying of solids and liquids, without evidence of mechanical obstruction.
- Common symptoms include nausea (92% of patients), vomiting (84% of patients), and early satiety (60% of patients).
- Gastroparesis has been observed among people with migraine during attacks, and possibly between attacks.
Functional Dyspepsia

- Functional dyspepsia is characterized by epigastric pain and early satiety in the absence of structural problems.
- Prevalence of functional dyspepsia is 10% (Rome IV) in the general population.
- In one study of people with functional dyspepsia, 68% had migraine.
Irritable Bowel Syndrome

- IBS is a chronic functional bowel disorder characterized by altered stool form or frequency in association with abdominal discomfort or pain.
- Traditionally divided into four subtypes based on the predominant stool pattern.
- Prevalence of IBS is 3.8% (Rome IV) to 9.2% (Rome III) in the general population.
- IBS is 2-2.5 times more common among people with migraine.
Abdominal Migraine

- Stereotypical, recurrent, attacks of moderate to severe midline abdominal pain (without headache) interspersed by symptom free periods
- Affects 2-4% of children, often around 7 years of age, with a slight female predominance
- Commonly progress to migraine later in life
  - Can occur in adults
Migraine Triggers: Diet

- Hunger, fasting, alcohol, certain foods, or additives (in foods or drugs) may trigger migraine
- Controversial: can food allergy trigger migraine or can elimination diets relieve migraine?
- The most common cause of “food allergy” is “food aversion” -- a psychologic response to the food itself
Migraine: Food Triggers

Lactose deficiency
• Common genetic disorder
• Symptoms
  – Abdominal cramps, flatulence
  – Perhaps headache

Red wine
• Those who believed that red wine, not alcohol, → headache given red wine or vodka
  – Red wine triggered migraine in 9/11
  – Vodka triggered migraine in 0/11
  – No headache in other migraine subjects or controls
• Alcohol itself may trigger migraine in other susceptible migraineurs

Littlewood, Lancet 1988
Migraine: Food Triggers

Monosodium Glutamate
• Produces migraine-like headache
• Responsible for Chinese restaurant syndrome

Chocolate
• Migraineurs who believed that it triggered their migraine were challenged with chocolate
• D-B,P-C study chocolate did not consistently trigger headache
• Chocolate on its own rarely triggers migraine
Probiotics: Systematic Review

• Evaluated impact of **probiotics** on frequency and severity of migraine attacks

• Methods: A systematic review was conducted to identify studies published up to October 2019. Meta-analysis of eligible trials performed using random-effects model to estimate pooled effect size.

• Results: Three randomized controlled trials with 179 patients (probiotic group = 94, placebo group = 85) were included.

  Probiotic supplementation had no significant effect on frequency (weighted mean difference (WMD) = −2.54 attacks/month, 95%CI: −5.31–0.22, p = 0.071) and severity of migraine attacks (WMD = −1.23 visual analog scale (VAS) score, 95%CI = −3.37–0.92, p = 0.262) with significant heterogeneity among the studies (I² = 98%, p < 0.001).

• Conclusions: Pooled analysis showed that probiotic supplementation had no significant effect on the frequency and severity of episodic migraine attacks
Artificial Sweeteners Alter Gut Bacteria in Humans

By Shafaq Zia

When consumed for as little as two weeks, common alternatives to sugar affect intestinal bacterial communities, with some reducing the body’s ability to regulate blood glucose levels, a study finds.
ROUTES OF DRUG ADMINISTRATION
Oral Route

ADVANTAGES
1. Convenient, noninvasive and easy to take
2. Usually good absorption

• DISADVANTAGES
1. Slow absorption
2. Irritable and unpalatable drugs- nausea and vomiting
3. Some drugs destroyed
4. First-pass effect- Due to Biotransformation
5. Food–Drug interactions and Drug-Drug interactions
Advantages Of Nasal Drug Delivery Systems: Administration of drugs directly into the nose

- Easy, convenient, self administration
- Rapid absorption and onset of action
- Hepatic first pass metabolism absent.
- Avoidance of GI irritation.
- Availability of large nasal mucosal surface area for dose absorption.
- Degradation of drug observed in GIT avoided
- Bioavailability of large drug molecules can be increased by means of absorption enhancers.
- Alternate to parenteral route
Targeting The Upper Nasal Space

TRADITIONAL NASAL PUMPS

POD® TECHNOLOGY

Anterior ethmoidal artery

Sphenopalatine artery

Posterior ethmoidal artery

Anterior ethmoidal artery

Sphenopalatine artery

Posterior ethmoidal artery